A STUDY OF ALTERATION IN THE LEVELS OF PLASMA FREE FATTY ACIDS AND BLOOD SUGAR WITH INHALATIONAL ANAESTHESIA

THESIS

FOR

M. D. (ANAESTHESIOLOGY)

BUNDELKHAND UNIVERSITY,
JHANSI (U. P.)

1984

PRAMOD KUMAR SINGH CHAUHAN

D E D I C A T E D

This work of ceaseless tire spread over
365 days, 5 hours, 59
minutes & 60 seconds,
Personally to the Third Chamber of the
Democratic Republic of
INDIA for
many private reasons;
Professionally to The ever-ailing Humanity
in the hope that some day
it might take away some of
its sufferings.

C E R T I F I C A T E

This is to certify that the work entitled " A STUDY OF ALTERATION IN THE LEVELS OF PLASMA FREE FATTY ACIDS AND BLOOD SUGAR WITH INHALATIONAL ANAESTHESIA " being submitted as thesis for M.D. (Anaesthesiology) examination, 1984 of Bundelkhand University, Jhansi was undertaken by Dr. Pramod Kumar Singh Chauhan in the department of Anaesthesiology in this institution.

He has put in the necessary stay in the department as per the University regulations.

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M.D., D.A.
Professor & Head of the Department,
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M.L.B. Medical College, Jhansi.

C E R T I F I C A T E

This is to certify that the work entitled " A STUDY OF ALTERATION IN THE LEVELS OF PLASMA FREE FATTY ACIDS AND BLOOD SUGAR WITH INHALATIONAL ANAESTHESIA" ; which is being submitted as thesis for M.D. (Anaesthesiology) examination, 1984 of Bundelkhand University, Jhansi by Dr. Pramod Kumar Singh Chauhan; has been carried out under our guidance and supervision.

The techniques and statistics used, were undertaken by the candidate himself. The same were checked by us from time to time.

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"M I L G R A C I A"

(Lest I may forget)

"Words are expressions unto themselves !"

Friends often ask me, " Have you ever been in an embarassing situation ?" I find myself in the midst of one right now.

Ironically for me, words seldom were expressions unto themselves and they still are not . I sincerely hope that peoples will understand my plight.

He is an unassuming simple man, who graced this work of mine by consenting to supervise the study even at his personal inconvenience. Pragmatic approach to the problem, calm and cool appreciation of the scenerio, dynamic agility to take swift and right decisions & unfathomable capacity of reasoned analysis of the facts coupled with a finely honed intuitive sense of "when to drive along and when to let go " are only few of his assets which unveiled themselves during the course of present study. One can feel the all-pervading imprint of his unique personality inculcated right to the very core of this work. He is Dr. S.L. Srivastava, Reader in the department of Anaesthesiology, M.L.B. Medical College & Hospital, Jhansi.

I find this to be the most opportune moment to pay my humble tribute to his splendid navigation in directing my efforts to impart some semblence of a presentable work to this thesis of mine.

During those fateful days of hectic activity, Dr. L.D. Joshi, Reader & Head of the department of Biochemistry, M.L.B. Medical College & Hospital, Jhansi, had been at his terrific best in between his trips abroad. I freely drew upon his vast repertoire of sound knowledge of human biochemical intricacies, recent advances and latest relevant data. I benefitted immensely from his expertise and hereby I do express my respect and gratitude duly accrued to him.

Whenever in future (at my leisure), may I be fortunate enough to focus my ken on this work, I will be overwhelmed with the fond remembrance of a young and bright lecturer in the department of Anaesthesiology in this institution whom people call Dr. Pradeep Sahi. The present work is his brain-child and he strove unusually hard, to shape the things to come, with his customary gay abandon. Correction, he proved to be the infrastructure- personified of this study. He was always brimming with some original yet concrete suggestions. He was quick and ever- agile to pindown and eliminate the flaws as and when they surfaced. On the other hand, he was equally swift and nimble-footed to step on my toes, if I were found lacking. His mere presence was my greatest asset and even the thought of his non- availability used to send quite a few chills down my spine.

I bow my head in pious reverence to the hermetic figure of Prof. B.C. Joshi, Head of the department of Anaesthesiology, M.L.B. Medical College & Hospital, Jhansi, who was considerate enough in allowing me to carry out the present study in the department. Surprisingly, in spite of frail health, he proved to be towering lighthouse of inordinate glitter and illumination, which even from a

distance was enough to navigate safely my hurricane venture in the Pacific of confusing (and often conflicting) data.

Drs. U.C. Sharma, D.D. Verma, Chitra Tyagi and A. Kumar all lent their much-sought-after counsel without a hitch. Each of them, in their own ways, was instrumental in furtherance of my work. I express my deep respects and am grateful to each of them singularly and collectively.

I am thankful to all surgeons (of various specialities) and their respective junior doctors for their inconvenience and understanding.

Dr. J.B. Singh, Lecturer in Biochemistry has lent his helping hand to me from time to time and placed vast resources at my disposal most generously. He always spared some time for me despite his crowded schedule. It has been a real pleasure for me to be so close to him.

Many collegues were inducted to help in smooth conduction of the present study and all of whom contributed his/her bits in one way or other. I rerely dared to defy their combined disfawour on any point, factual or syntectical. Fortunately (for me), they often differed; this gave me the advantage of being able to do as I liked. It is a pleasure to aknowledge my sincere gratitudes to Drs. Girish Nigam, Ravi Shukla, P.C. Srivastava, Dileep Saxena, P.N. Singh, Mukesh Garg, Ashok Hasija, Anil Agarwal, Pradeep Lakhani, N.K. Gupta 'Nandu', Pradeep Khattri, Prem Kr. Singh, Awadhesh, Ram Nath, S.P.K. Bhullar, R.K. Tripathi, Ashok Saxena, S.C. Agarwal, Vasudev Lala and many others.

Sri B.K. Saxena (O.T. Master), all staff nurses (particularly Km. Anita Yakub and Km. Anna M. Patrick) , all technicians and all

attendents/wardboys of Operation Theatre tried their best, as did Sri Balmukund Sharma (technician Biochemistry) and his team mates, to make my monotonous ordeal a pleasant one.

All the patients (who formed the nucleus of my study) and their family members deserve my deep sense of gratitude for their ability to suffer inconveniences with a sporting gesture.

Sri Rajendra Prasad proved his elite cadre by preparing a beauty of a typescript in a rather short period.

I tender my unequivocal apologies to all authors and publishers etc., the copy-rights of whom I may have infringed inadvertently and without motive.

My parents, brothers and sisters were put to a lot of inconveniences by me. Yet, they were always there, when I needed them most. I find no words expressive enough to release the cache of my emotions directed towards them, but they have always under stood. They will still understand.

To all of you, I can only say " THANK YOU ".

JHANSI

30. 5 . 1983

(P.K.S. CHAUHAN)

CONTENTS

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INTRODUCTION

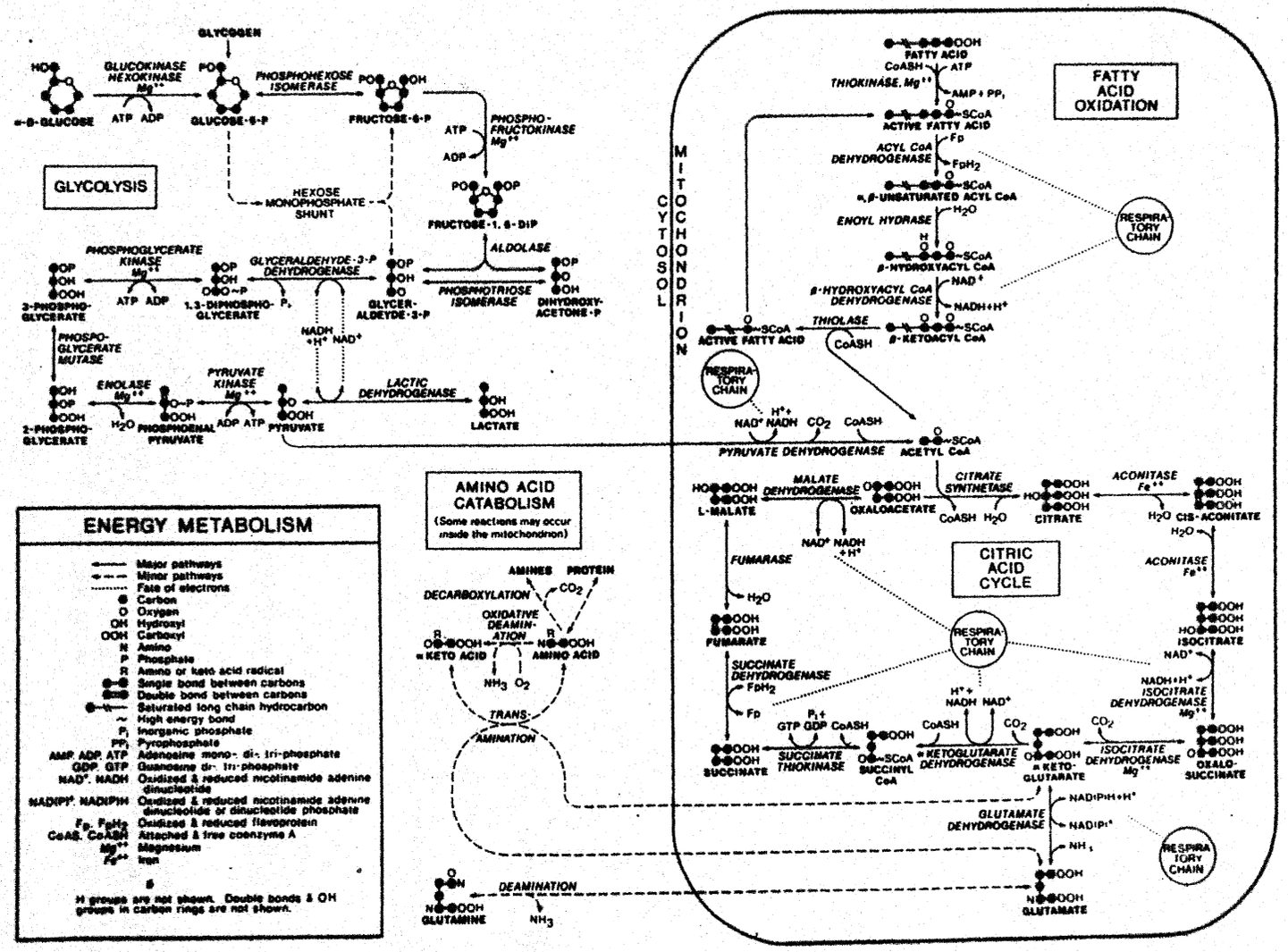

FIG. 1 - THE ENERGY METABOLISM.

INTRODUCTION

"We have observed from the standpoint of anaesthesia that a curve of reflex irritability follows a course paraller to that of metabolism. Cell oxygen demand, of course, is the same curve as that of metabolism".

Arthur Guedel, 1924.

Everything under (and over) the Sun has a darker side (similar to the other side of a coin) and anaesthesia is no exception.

The never-ending human quest towards minimizing the mortality and morbidity in seriously ill or traumatized patients has resulted in more and more attention being paid to the matabolic stability. Proper maintenence of the metabolic needs of the patient has emerged as perhaps the single most important factor in improving the chances of survival in such patients.

The giant strides made in the field of anaesthesiology in the current century, render a whole spectre of agents and techniques to the modern anaesthetist for providing excellent operating conditions. But even in the present era of "balanced anaesthesia", almost all anaesthetic agents, whether intraveneous or inhalational, extol their price by producing variable but significant derangements in the metabolic homeostasis. In the past, everyone was sceptical of anaesthesia in the mistaken notion that it alone is responsible for causing all the metabolic upset, but recent sophisticated techniques and interpretation of earlier data in the right perspective have helped the anesthetist to breathe easy, while the surgery itself has come in for some really nasty criticism for being the real culprit.

The metabolism, at its simplest form, consists of supply of metabolic fuels and their conversion into chemical energy for cellular

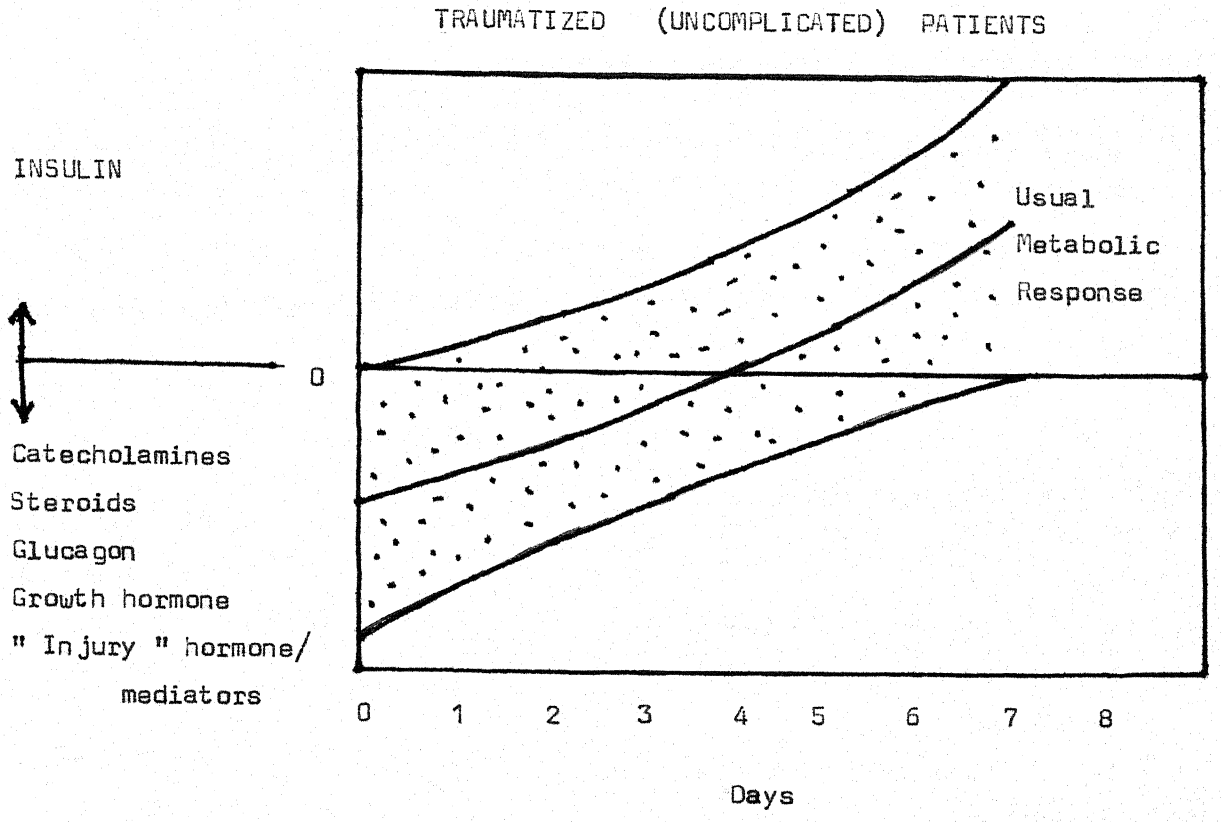

FIG. 2 - THE ENDOCRINE RESPONSE TO TRAUMA

The usual metabolic response to major accidental/ surgical trauma includes an initial phase characterized by the catabolic hormones. Adaptation occurs after 3 - 5 days.

functions, the various fuels being carbohydrates (glucose, fructose and galactose), lipids (mainly triglycerides) and proteins (alanine and glutamine).

The human metabolism is peculiar in that some tissues (red blood cells) are totally dependent while others (brain and renal cortex) are partially depentent upon glucose for energy production, therefore blood glucose concentration needs to be maintained within relatively narrow limits. On the other hand, the total carbohydrate reserve of the body is less than even a single day's basal metabolic requirement.

Glucose, being the most active fraction of carbohydrates, is utilized by the tissues for energy production. Upto mild degree of stress or exercise, glucose alone may meet the energy demand, But beyond certain limits the fatty acids activity comes into play to meet the additional requirement for energy production. A fall in the blood glucose concentration results in lipolysis and free fatty acids (FFA) are released in the blood. This FFA fraction, though only 5% of total plasma fatty acids, has a very rapid turn-over rate. The FFA are carried in the plasma as an "Albumin-FFA complex" to the tissues for energy production.

Immediate survival of body in acute stress-situations may well depend upon how much and how rapidly the body can mobilize its metabolic resources. Anaesthesia is one acute clinical stress of iatrogenic origin, which affects carbohydrate and lipid metabolism to a variable degree.

Surgery is another step ahead. Any surgical trauma in itself causes profound changes in metabolism; while a combination of previous injury, surgical trauma and anaesthesia results in profound and long-lasting metabolic changes, the most apparent being the hyperglycemia. The extent of this hyperglycemia is a crude but effective indicator of the stress-response shown by the body. The duration of anaesthesia and surgery also affects the degree of metabolic mobilization and hyperglycemic response.

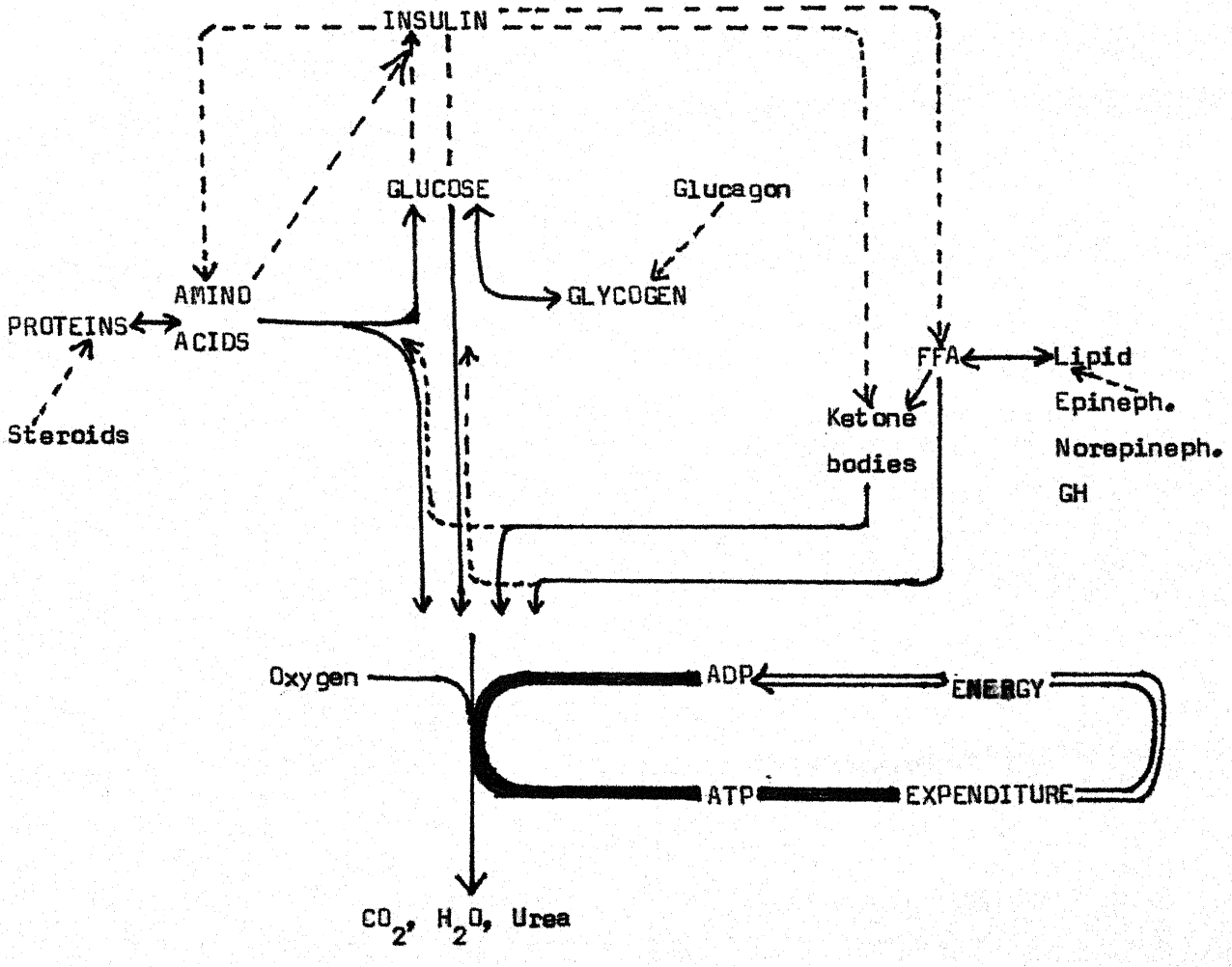

FIG. 3 - METABOLIC FUEL REGULATORY SYSTEM

Arrows indicate how the metabolic fuels and insulin influence each other's concentration in blood. The metabolic pathway for the oxidative degradation of the various fuels lead to common terminal events. The oxidation of metabolic fuels occurs in an integrated fashion, so that the total energy generated is equal to the energy expenditure (ATP/ADP) ratio.

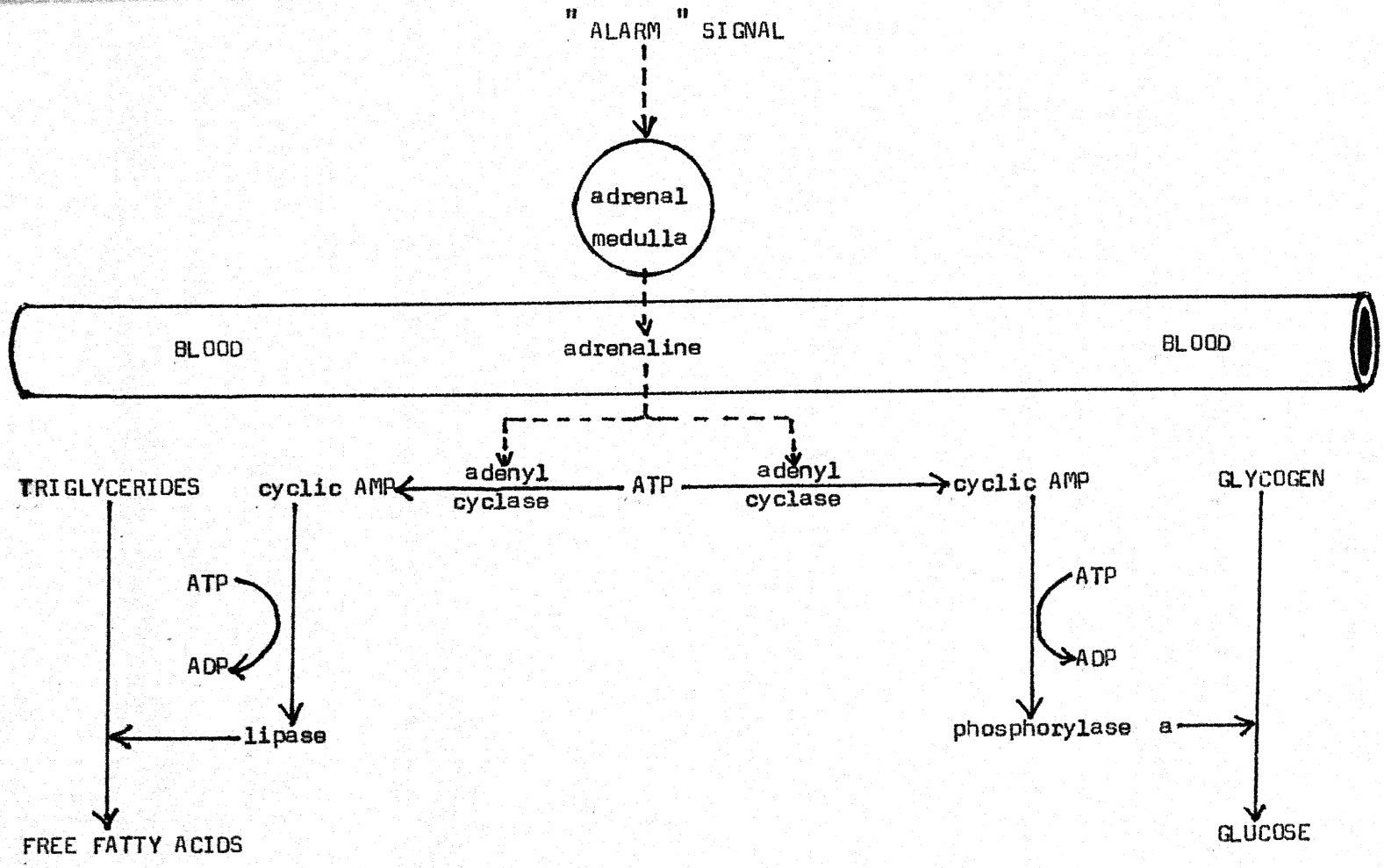

Fig. 4 - The adrenal medulla is stimulated to release adrenaline into the blood by signals from the central nervous system. Adrenaline activates adenyl cyclase, which catalyzes cAMP. Cyclic AMP triggers the actions of phosphorylase a and hormone sensitive lipase which results in conversion of glycogen into glucose and triglyceride into FFA. A little adrenaline has a large effect according to Rube Goldberg sequence.

The hyperglycemic response seen during and after injury, anaesthesia and surgery is on account of increased glycogenolysis and gluconeogenesis (i.e. endogenous glucose production from non-carbohydrate substrates).

The levels of glucose and FFA in the blood and their inter-relationship reflects the degree of hyperglycemic - hyperdynamic metabolic response which in its turn is directly proportionate to the degree of stress, which the body is undergoing at that time; therefore circulating concentrations of glucose and FFA in blood help to assess the degree of stress, which the patient undergoing anaesthesia and surgical trauma is subjected to.

The present study aims at studying the alterations in blood sugar level (a good parameter to judge extent of carbohydrate metabolism) and plasma FFA (most active fraction of fatty acids and with a very rapid turn-over rate, hence a good parameter to judge extent of lipid metabolism) during inhalational anaesthesia with and without surgery and to assess the various inhalational anaesthetic agents in relation to the changes in these parameters.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

The function and life of cells depend upon the ability of the organism to produce and store chemical energy and its conversion to cellular work by the process of metabolism.

Anaesthesia is an induced state where the chemical anatomy within the living body is dismantled to a variable degree (Bose and Biswas, 1981). They also observed (1981) that carbohydrate and lipid metabolism are two pivotal components of the biochemical architecture, most vulnerable to affection in anaesthesia.

There is an increasing awareness that anaesthesia alone is not responsible for the metabolic changes, but surgical trauma also plays a role in the stress-response (Griffith 1953, Cullingford 1966 and Clarks 1968, 70).

In order to understand and appreciate the complex stress response of the body to anaesthetic and surgical trauma, it is better to refresh our memory with a few glimpses at the human metabolism with an eye being kept on carbohydrate and lipid metabolism.

Intermittent dietary intake in presence of continuous utilization of nutrients by the tissues, makes it mandatory for the body to have a good reserve store of such nutrients. The total resources available to an average human (70 kg. body weight) are as follow:-

Total calories = 126000 Kcal.

Daily dietary intake = 2% of above reserve.

A detailed table showing the full break-up of this reserve store is given on next page.

Fuel	Tissue	Fuel reserves in a 70 kg. Man		
		Kcal.	Gm.	Percent
Triglyceride	Adipose Tissue	100000	15000	80
Glycogen	Liver	200	70	1
	Muscle	400	120	
Glucose	Body fluids	40	20	
Proteins	Muscle	25000	6000	19

(Plus 2% of this reserve as daily dietary intake = 2500 Kcal.)

(Newsholme and Start, 1973)

It is important that atleast one of these fuels is always available to the body. It is also imperative that the rate of production of each fuel be regulated precisely to the rate of its utilization and the rates of production and utilization of all fuels be integrated satisfactorily.

The metabolism of higher animals suffer from several disadvantages:-

(1) Some tissues (RBCs) are totally dependent while others (brain and reanal cortex) are partially dependent upon glucose as the only metabolic fuel. Therefore adequate supply of glucose to such tissues must be maintained at all costs.

(2) The capacity of liver to store glucose as glycogen is limited, while adipose tissues store enormous quantity of triacylglycerol.

(3) Higher animals are unable to synthesize glucose from fatty acids and therefore can not utilize this huge store of triacylglycerol, which dose however contribute to glucose supply directly by providing

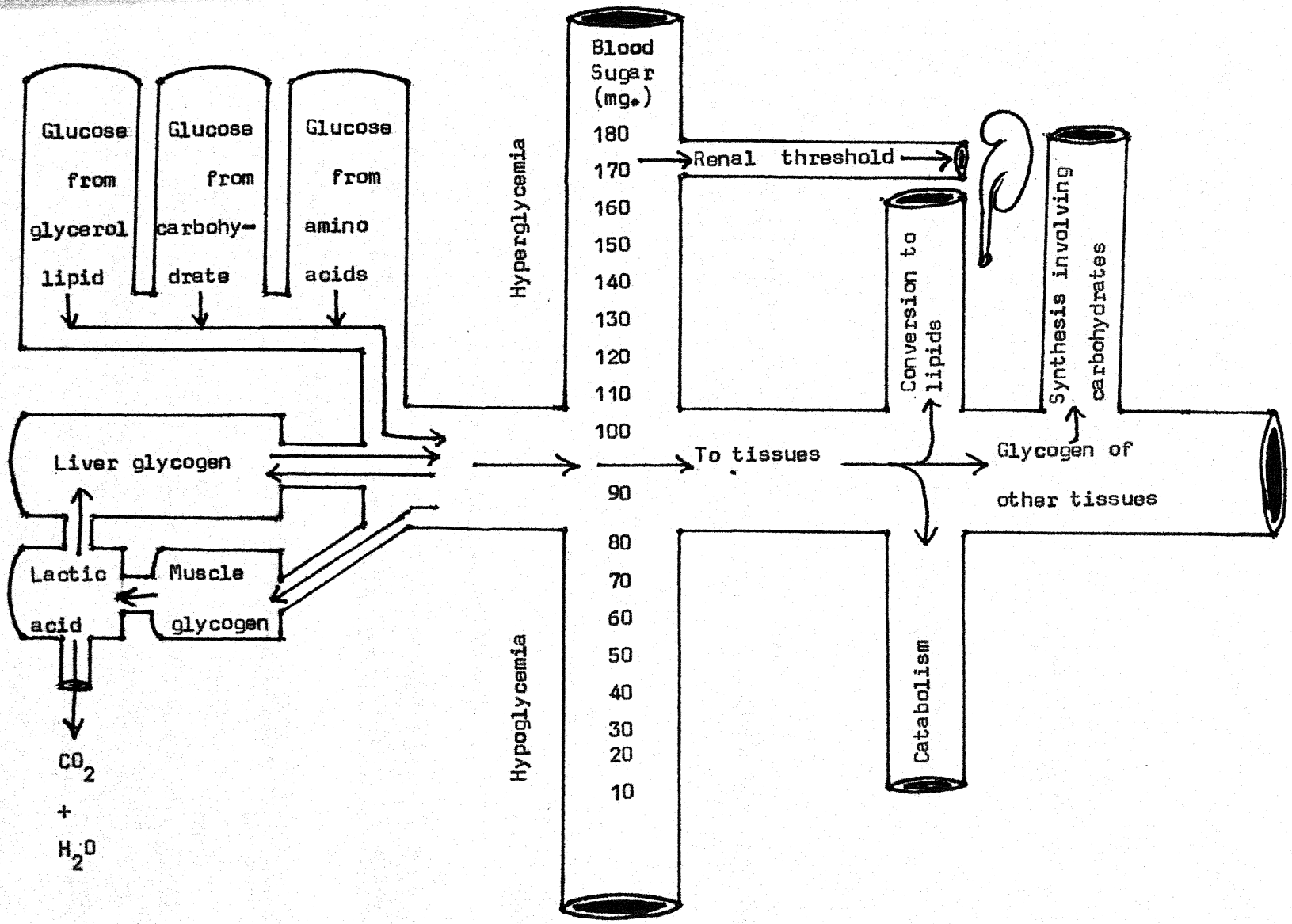

FIG.5 - ORIGIN AND DISPOSITION OF BLOOD SUGAR.

glycerol (a gluconeogenic precursor) and indirectly by providing fatty acids (FA) and ketone bodies (KB).

INTERMEDIARY METABOLISM OF CARBOHYDRATES

The chains of reactions that occur in body during the process of carbohydrate metabolism are as follow:-

1. Glycogenesis - It is the synthesis of glycogen from glucose to be stored in the body. Glucose is phosphorylated by hexokinase plus ATP to form glucose-6-phosphate (in the liver the enzyme is glucokinase). G-6-P is then converted to G-1-P under the influence of enzyme phosphoglucomutase. G-1-P reacts with uridine triphosphate (UTP) to form uridine diphosphate glucose (UDPG) which is converted by polymerization to glycogen under influence of enzyme glycogen synthase. The glycogen synthesis is promoted by insulin.
2. Glycogenolysis - Glycogen breakdown is brought about mainly in the liver to form glucose. The enzyme adenyl cyclase is first activated and catalyses the formation of cyclic AMP from ATP. This converts inactive phosphorylase to active phosphorylase which forms G-1-P from glycogem, the former being converted to G-6-P by phosphoglucomutase. G-6-Phosphatase converts G-6-P to glucose in liver (but not in the muscles) and promotes its entry in blood. Since muscles do not contain G-6-Phosphatase, G-6-P formed in the muscles enters either the Embden-Meyerhof or hexose monophosphate pathway to yield lactic acid as its final product.
3. Glycolysis - Oxidation of glucose or glycogen leads to formation of G-6-P which enters the Embden-Meyerhof pathway to yield the end products, lactate and pyruvate. The glycolysis is controlled by the rates of hexokinase and phosphofructokinase reactions (Lowry et al, 1964).

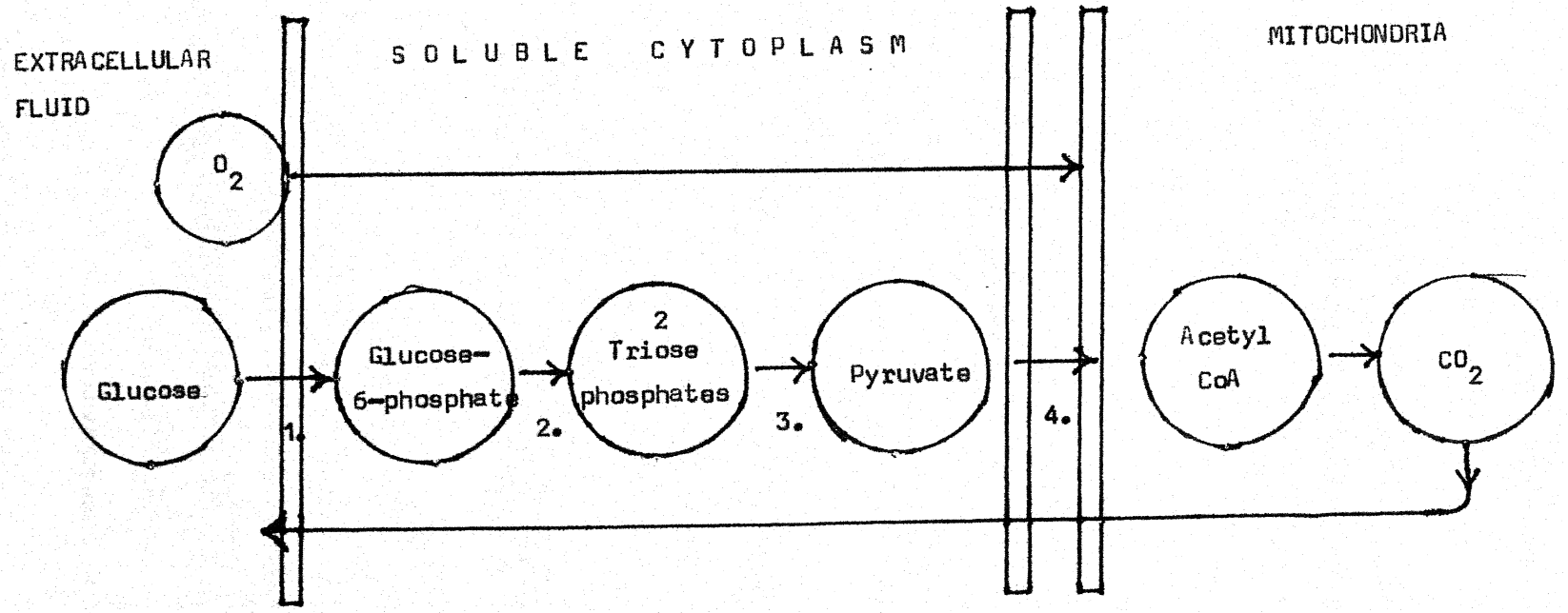

FIG. 6 - GENERAL OUTLINE OF THE OXIDATION OF GLUCOSE. 1. The absorption of glucose by cells, followed by the formation of glucose-6-phosphate, 2. the transformation of glucose-6- phosphate into 2 molecules of triose phosphates, 3. conversion of the triose phosphates into pyruvate, 4. the oxidation of pyruvate to acetyl CoA which is then oxidized by the TCA cycle.

4. Tricarboxylic Acid Cycle - Also known as Kreb's cycle or citric acid cycle. It is the final common pathway for oxidation of carbohydrate, lipid and protein. The pyruvate formed at the end of glycolysis converts to oxaloacetic acid which combines with acetyl CoA to yield citric acid, alpha-Ketoglutaric acid, succinic acid and finally oxaloacetic acid. In the whole process acetyl CoA is completely oxidized to carbondioxide and water with liberation of energy at various stages in the form of ATP. The oxaloactic acid reformed again enters the cycle by combining with another molecule of acetyl CoA.

5. Hexose Monophosphate Shunt - This is a direct oxidative pathway and serves as an alternative to Embden-Meyerhof pathway and Kreb's cycle. Here G-6-P is directly oxidized to carbondioxide and water with liberation of energy.

6. Gluconeogenesis - It is the formation of glucose from non-carbohydrate substrates. According to Stanley (1981) , It operates :-

(i) By minimizing oxidation of glucose by recycling precursors (lactate) and via exchange reactions (alanine, glutamine).

(ii) By de-novo synthesis.

The lactate and alanine are converted into pyruvate, and glycerol into a triose-phosphate.

Gluconeogenesis and glycolysis are the reverse processes and enzymes unique to either pathway, oppose those of other pathway at three sites.

When liver glycogen stores are exhausted (starvation, stress), Gluconeogenesis is the only endogenous source of glucose

supply; the major sites being liver and renal cortex, while the major precursors are lactate (derived from anaerobic tissues e.g. RBC, renal medulla, testis, anaerobic respiration of glucose in muscles), glycerol (derived from lipolysis in adipose tissue), alanine and glutamine (derived from protein breakdown in muscles). Amongst amino acids, liver uses alanine while renal cortex utilizes glutamine. Efficient gluconeogenesis requires integrated metabolism of various tissues either supplying the precursors or producing glucose from these precursors. As the duration of stress (e.g. starvation) prolongs, the relative importance of liver as site of gluconeogenesis decreases, while that of renal cortex increases.

Gluconeogenesis from amino acids or glycerol represents a net gain of carbohydrate for the body, while that from lactate merely involves recycling of carbohydrate. The energy for this conversion is derived at the expense of fatty acids.

BLOOD GLUCOSE REGULATION

The blood glucose level at any moment represents an equilibrium between the rates at which glucose is entering or leaving the blood stream. Numerous factors contribute to the homeostatic processes which keep the blood glucose level constant within relatively narrow limits.

The final products of digestion pass through the portal vein to the liver where fructose and galactose are converted to glucose. Liver serves as a receiving, manufacturing, storing and distributing centre for glucose which is then carried in the blood stream to all parts of the body. The secretion of glucose from the liver tends to raise the blood glucose while its

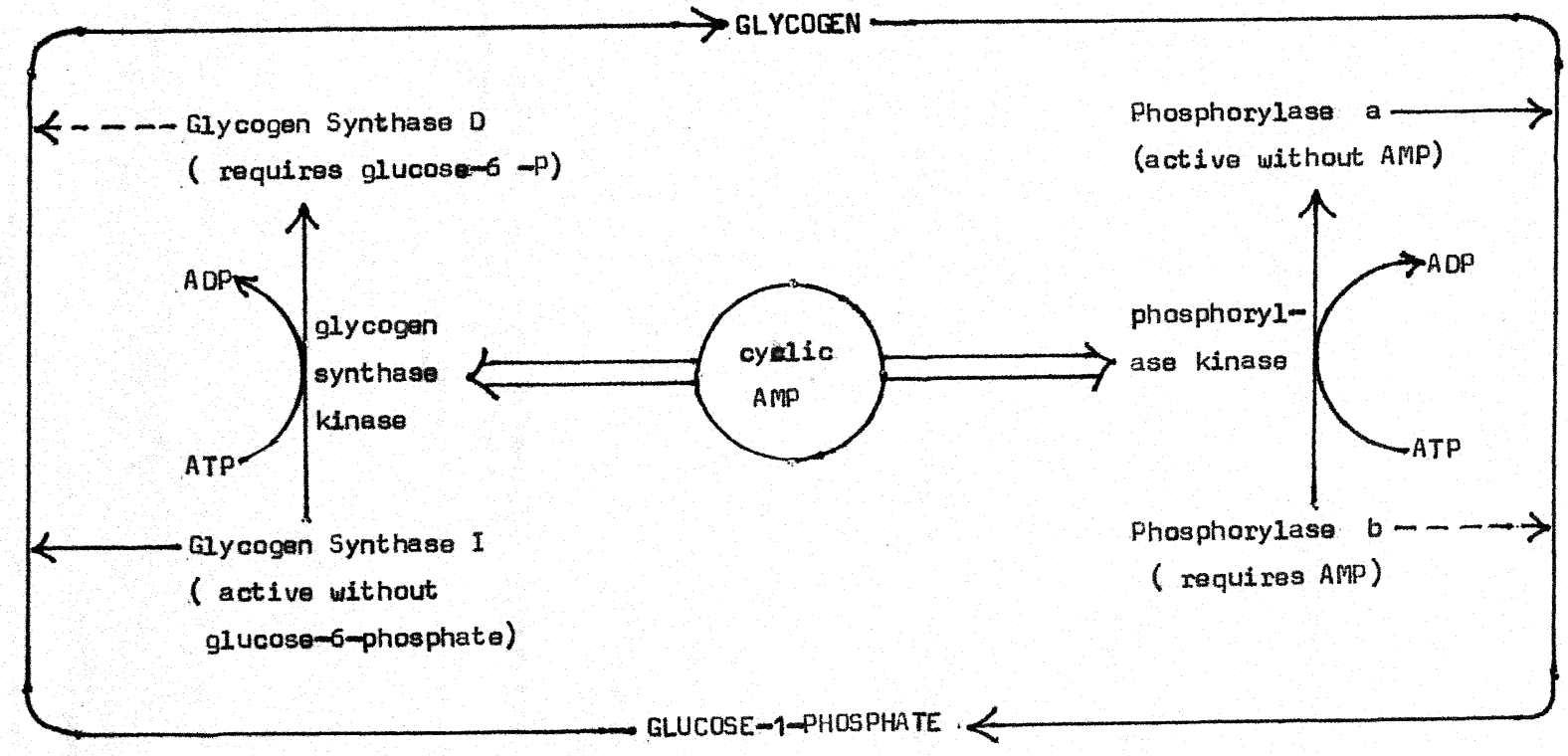

Fig. 7 - Interconversion of glycogen and glucose-1-phosphate depends on the presence or absence of cyclic AMP. Without cAMP, the critical enzymes are in non-phosphorylated forms; glycogen synthase is independently active (solid arrow), while phosphorylase b is inactive (dashed arrow) unles a rise in 5' - AMP concentration signals a deficit of high energy phosphate.

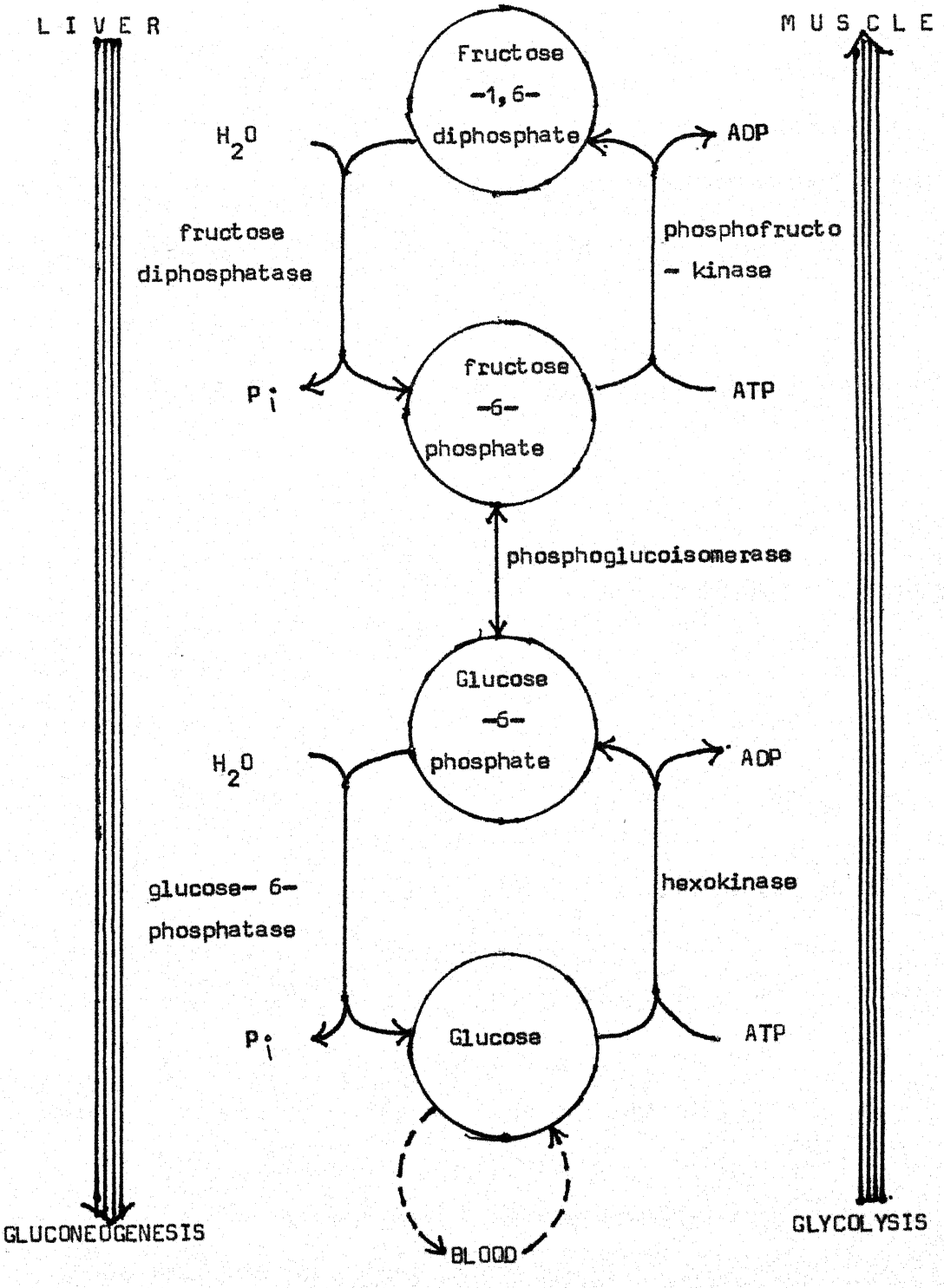

Fig.8 - The interconversion of fructosediphosphate and glucose occurs by different routes in liver and muscle. Fructose diphosphate is converted to glucose in liver which diffuses into the blood.

removal by actively metabolizing tissues tend to lower it.

Liver cells are freely permeable to glucose, so the liver is capable of speedy responses to changes in blood glucose concentration. This, it self can determine whether the liver is a glucose-producing or glucose-using organ and at what rate glucose is taken up or released by this tissue (Soskin et al, 1938).

Enzyme glycogen synthase promotes conversion of glucose into glycogen, while glycogen phosphorylase and G-6-Phosphatase favour conversion of glycogen into glucose. The in-vivo equilibrium of these opposing enzymes is responsible for maintaining sufficient blood glucose concentration (Stalmans, 1976). Hepatic cellular responses to fluctuations in blood glucose level are also controlled by intermediary metabolites, ratios of oxidized to reduced co-enzymes, availability of ATP or ADP etc. These represent cellular processes independent of hormones. In addition, control by many hormones is superimposed on these more primitive control mechanisms.

Glucagon and beta-adrenergic agonists activate adenyl cyclase, thereby stimulating the cAMP dependent proteinkinase which, in its turn, activates enzyme glycogen-phosphorylase and by resultant glycogen breakdown, raises the blood glucose level (Stanley, 1981).

Some other hormones (alpha-adrenergic agonists, vasopressin, oxytocin, angiotensin II) act in a different manner. They increase the level of mitochondrial calcium ions within liver cells with consequent stimulation of phosphorylase-b-kinase. The latter accelerates glycogen breakdown and increases glucose level in the blood (Stanley, 1981).

Insulin antagonises the action of all the above hormones. The machanism of insulin action is not well understood, but one attractive possibility is that it stimulates one or more of the protein phosphatases

(Hems and Whitton, 1980; Stanley, 1981).

Factors which tend to raise blood Glucose	Factors which tend to lower blood Glucose
Hunger	Satiety
Glucose absorption from G.I.T.	Glucose diffusion in E.C.F.
Hepatic Glycogenolysis	Muscular exercise
a) Adrenaline	Insulin :
b) Glucagon	Increased Glucose oxidation
Gluconeogenesis	Increased glycogen deposition
Insulin antagonists	Increased lipogenesis
a) Growth hormone	Decreased gluconeogenesis
b) Cortisol	Glycosuria (in diabetic patients)
Insulin destroying enzymes	MJ 1999 (by inhibiting adrenaline)

INTERMEDIARY METABOLISM OF LIPIDS

This consists mainly of metabolism of lipid storage site (i.e. adipose tissue), lipolysis, mobilization of fatty acids and their utilization.

1. Adipose tissue and its metabolism: Triglycerides account for about 90% of adipose tissue (Boyd and Lowe, 1957). This tissue is shown to metabolize glucose by the glycolytic, phosphogluconate and glucuronic acid pathways (Vaughen 1961, Winegrad 1962), to carry out de-novo synthesis of FA and to synthesize triglycerides. These processes and their hormonal control represent an important regulatory component of

the overall carbohydrate and fat metabolism of the body.

Adipose tissue capillary endothelium liberates "lipoprotein lipase" which is responsible for release of free fatty acids (FFA) from circulating "glyceride lipoprotein complex". Insulin and dietary carbohydrates stimulate the activity of this enzyme. Add itional lipase activity results in the breakdown of triglycerides (TG) to FFA and is influenced by a number of hormones. Adrenaline stimulates TG breakdown and release of glycerol and FFA (Hagen and Ball 1960, Winegrad 1962). Insulin increases FA and TG synthesis by possibly increasing the entry of glucose into the fat cell, which has very little capacity to phosphorylate glycerol and is dependent upon glycolytic production of glycerol phosphate for the formation of phosphatidic acids and TG.

Decreased glucose levels in muscle elicit an outflux of FFA from adipose tissue, which is carried to the tissues for energy production.

Uptake of blood glucose by the adipose tissue supply acetyl CoA units for adipose lipogenesis. Adipose tissue contains an oxidative system that forms carbondioxide and provides energy for FA and TG synthesis. Thus this tissue is a dynamic focal point of lipid metabolism.

2. Fatty acid mobilization : Following intracellular hydrolysis of triacylglycerol, FFA are released into blood. Due to relative insolubility, they are transported in the blood bound to albumin (and to high density-, low density-, and very low density lipoproteins).

Triglyceride lipase is the "flux-generating" enzyme for hydrolysis of triacylglycerol (Newsholme and Crabtree, 1979). This generates the flux both by lipolysis, (in adipose tissue) and by FA oxidation (in muscles). A flux-generating enzyme has some characteristics:-

(i) It catalyses a non-equilibrium reaction in vivo.

(ii) It reaches saturation with its substrate in vivo.

(iii) It is independent of changes in the concentrations of pathway-substrates.

(iv) It responds only to factors external to the pathway.

(v) And most important of all, it generates a flux to which all other enzyme-catalysed reactions in the pathway respond.

Fatty acid mobilization increases during conditions of stress. Increased sympathetic activity with adrenaline release from the nerve endings stimulates cAMP dependent protein kinase via adenyl cyclase and cAMP. This results in activation of triglyceride lipase leading to hydrolysis of triacylglycerol with consequent increased FA mobilization.

Isotopic techniques reveal that a part of FA formed are again esterified to resynthesize triacylglycerol. This, despite being ATP-consuming reaction, provides a sensitive and delicate control over the mobilization of FA from the adipose tissue.

Catecholamines, glucagon, growth hormone (in presence of glucocorticoids and ACTH) and thyroid stimulating hormone tend to raise the FA level, while insulin and prostaglandins (PGE_1 and PGE_2) tend to lower the same.

Factors which tend to raise blood FA and FFA	Factors which tend to lower blood FA and FFA
Stress	Parasympathetic stimulation
Starvation	Satiety
Catecholamines	Insulin
Glucagon	Nicotinic acid
Growth hormone	Prostaglandins
Thyroid stimulating hormone	MJ 1999 (by inhibiting adrenaline)
Diabetis	

3. Free fatty acids : These are important vehicle of FA transport from adipose tissue depots to other tissues. The main sources of FFA are triacylglycerol, circulating lipid esters, intestinal chyle and liver. Exogenous triglyceride may account for 10% of FFA during the absorptive phase of fats (Fredrickson et al, 1958).

FFA exists at physiological pH mainly in form of acyl acids, but some anionic dimers may also be present in free solution in equilibrium with FA anions (Spector, 1968). The concentration of FFA in normal humans is about 0.5 mEq./litre (Goodman, 1958; Nutrition Review 1959) and a plasma half-life of 1 - 2 minutes corresponding to a fractional turn-over of 30% - 60% per minute (Fredrickson et al, 1957, 1958; Laurell et al, 1957). All transport of FFA between plasma and cells occurs through the small extracellular unbound FFA pool and this depends upon the concentration-gradients across the cell-membrane (Spector, 1968). This implies that FFA receptors on cell-surface have a very high affinity for FFA in comparision to albumin and the turn-over of the FFA pool takes place at an extraordinarily repid rate. But Zierler and co-workers (1965) were of the opinion that FFA is most probably transferred directly from binding sites on albumin molecules to acceptor sites on the cell surface, where FFA is an obligatory intermediary. They also demonstrated that outflow of FFA depends on the size of "cellular release FFA pool" and is not influenced by the concentration in the surrounding medium.

Hevel and associates (1963) using Palmitic-1-C^{14} as tracer Fatty acid in their experiment of treadmell walking at 3 - 4 miles per hour, obtained avarage turn-over rate of 27.7 mmol/minute during the sceond hour in human beings in the post-absorptive state, while the rate was only 7.6 mmol/minute in subjects who were fed carbohydrates in excess of their

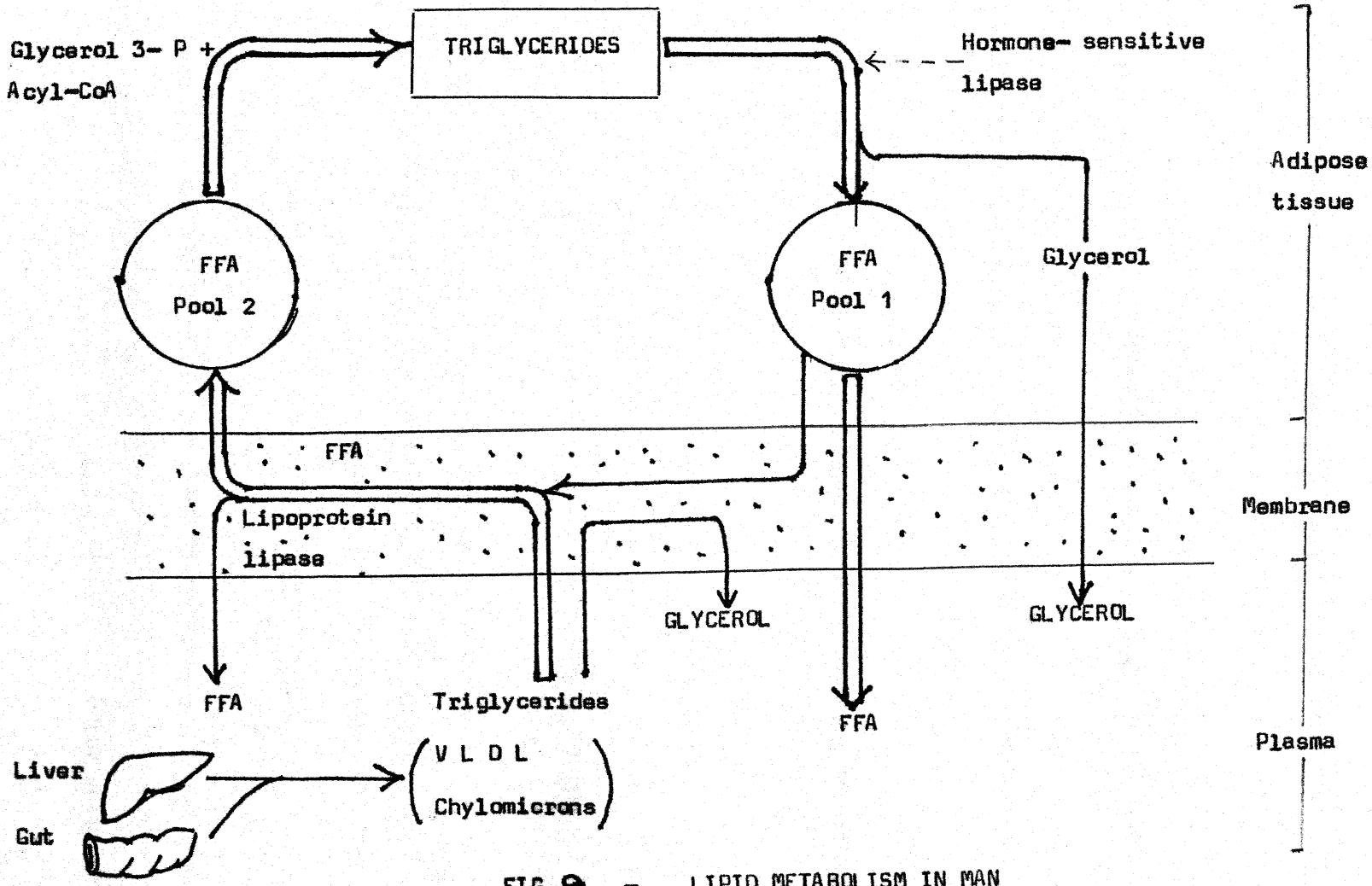

FIG. 9 - LIPID METABOLISM IN MAN

VLDL and chylomicrons are metabolised by lipoprotein lipase. The resulting FFA enters FFA pool 2 for rapid intracellular conversion to triglycerides. This pathway is stimulated by insulin and glucose. Hormone sensitive lipase releases fatty acid into the circulation.

energy needs.

Spitzer and Isseкutz (1964), by using arterivenous differences in FFA level on vessels supplying predominently muscles (or myocardium), showed FFA removal to the tune of 2 - 4 mEq/minute.

ENDOGENOUS CONTROL OF FFA METABOLISM

I. **Control mechanisms** - Circulating plasma FF^A level exerts single most important influence on FFA turn-over. Thus all hormonal and other influences that affect the release of fatty acids from adipose tissue (and thereby change arterial FFA level), will also alter the FFA turn-over (Armstrong et al, 1961; Isseckutz et al, 1964).

(A). Catecholamines- Increase the mobilization and turnover of FFA. This may account for the calorigenic effect of catecholamines. This calorigenic response may be composite of several factors, such as redistribution of various substrates (glucose, FFA, pyruvate, Lactate, glycerol, aminoacids), changes in the secretion of other hormones (glucocorticoids, insulin), an increase in the work of heart, increase in protein metabolism and redistribution of blood flow.

Nicotinic acid and "MJ 1999" inhibit catecholamine-induced increase in plasma FFA level (Svedmyr et al, 1967).

(B). Insulin - Insulin administration decreases FFA release (Armstrong et al, 1961). A feedbak of plasma FFA on insulin secretion is also present (Greenough et al, 1967; Madison et al, 1968). So acute elevation of plasma FF^A is followed by an increase in plasma insulin level.

II. **Fatty acid metabolism in various tissues** - FFA serve as the major transport form of lipid that supply oxidizable substrate to the

individual tissues. Because nearly all tissues can utilize fatty acids, the rate of FFA flux is very high, resulting in a complete turnover of the plasma FFA pool in a few minutes under controlled resting conditions. The breadk-up of FFA turnover is liver 35%, GIT 20%, Skeletal muscle 25%, Myocardium 6%, Kidney 5%, Brain 2%, others 7% (Spitzer et al, 1971).

(A). Myocardium - In the post-absorptive state plasma FFA serve as the major metabolite and may account for 60% - 100% of oxygen consumption by myocardium. Rest 30% - 40% are contributed by lactate and glucose. Presence of ketone bodies suppresses FFA utilization by this tissue.

(B). Skeletal muscle - FFA accounts for 25% - 30% of the energy metabolism in resting muscle. Muscle glycogen and ketone bodies become major metabolites during exercise. Ketone body infusion suppresses the uptake and oxidation of FFA.

(C). GIT - FFA accounts for 20% of energy production. Uptake and oxidation of FFA is proportionate to arterial FFA concentration.

(D). Liver - It utilizes 35% of total FFA flux. This portion does not alter with dietary status or diabetes. The fate of FFA entering the liver may be oxidation to carbon diaoxide or ketone bodies or synthesis to TG, phospholipids or cholesterol esters. FFA influx to the liver depends upon plasma FFA level and the balance between FFA and other substrates which can serve as respiratory fuel.

(E). Kidney - FFA is the most important energy substrate and it directly affects sodium reabsorption. Other important

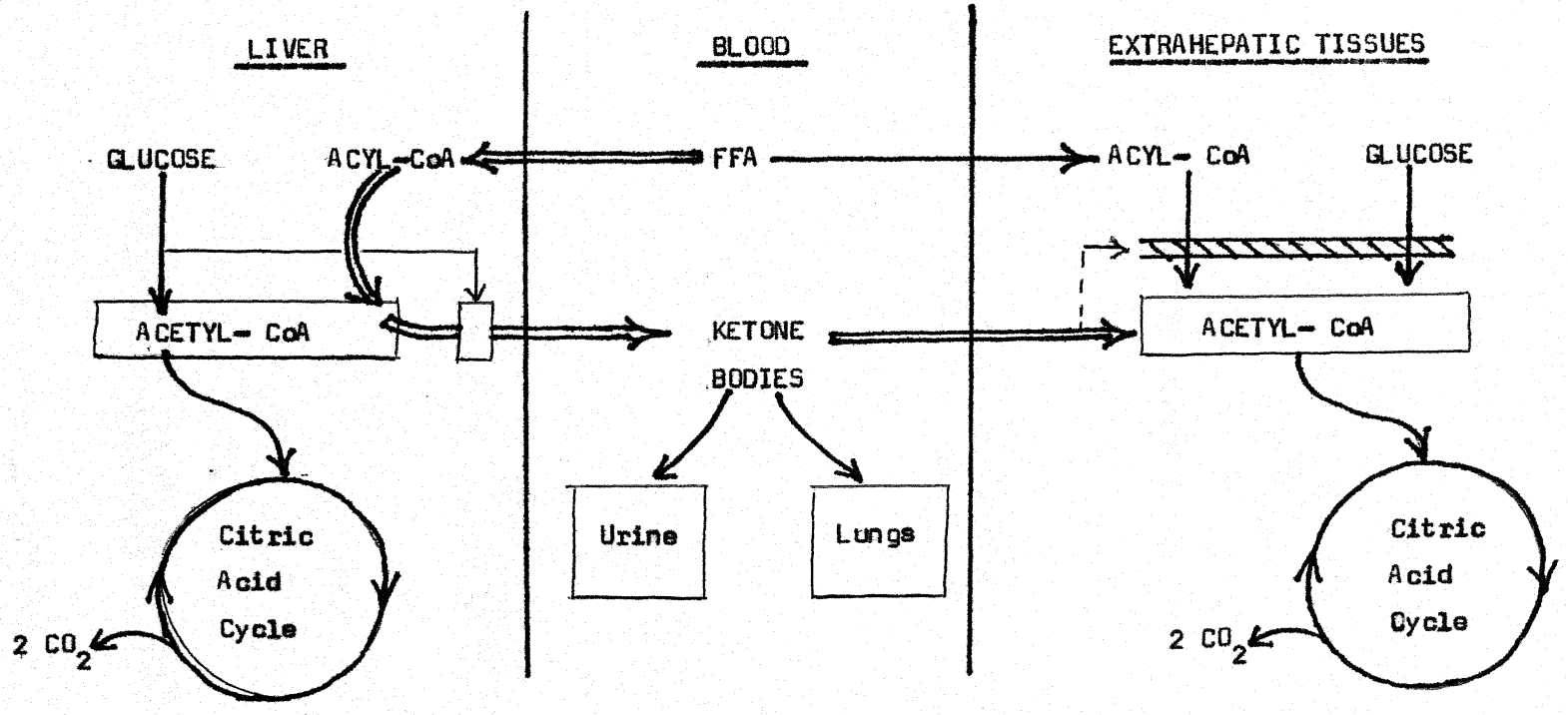

FIG. 10 - KETONE BODY REGULATION OF FFA METABOLISM

Partial oxidation of FFA to ketone bodies represents an effective disposal of FFA while providing ketogenic fuel for extrahepatic tissues. The result is sparing of glucose as a metabolic fuel.

metabolic substrates are KB, lactate, pyruvate and alpha-ketoglutarate.

(F). Brain - Possesses all the enzymes necessary for utilization of glucose, FFA or ketone bodies. Glucose is the major metabolite at rest, while during conditions of "physiological ketosis" (i.e. starvation, exercise, exposure to cold, child birth etc.), ketone bodies and FFA provide major portion of energy.

(G). Prostaglandins - PGE_1 and PGE_2 inhibit lipolysis and decrease the plasma FFA level by interfering with cAMP formation.

INHIBITION OF GLUCOSE UTILIZATION BY FATTY ACID OXIDATION

Fatty acid perfusion (in presence of glucose) inhibits the rate of glucose uptake and glycolysis in isolated rat heart (Garland et al, 1964) and in red skeletal muscles (Rennie and Holloszy, 1977) provided that the preparation is well oxygenated. Thus in heart, diaphragm and red skeletal muscles, fatty acids are not only oxidized in preference to glucose but they also inhibit glucose utilization.

During starvation or severe exercise the blood FA level increases while respiratory quotient decreases from 0.81 to 0.73 indicating a shift from carbohydrate to lipid utilization.

$$R.Q. = \frac{\text{Rate of } CO_2 \text{ output}}{\text{Rate of } O_2 \text{ Uptake}}$$

$$C_6H_{12}O_6 + 6\ O_2 \longrightarrow 6\ CO_2 + 6\ H_2O = 6/6 = 1.00$$

$$C_{57}H_{104}O_6 + 80\ O_2 \longrightarrow 57\ CO_2 + 57\ H_2O = 57/80 = 0.71$$

$$2\ C_3H_7O_2N + 6\ O_2 \longrightarrow (NH_2)_2\ CO + 5\ CO_2 + 5\ H_2O = 5/6 = 0.83$$

This shift occurs without any marked decrease in blood glucose level and implies that lipid- derived fuels are being oxidized in preference to glucose. Hence FA oxidation inhibits glucose utilization or oxidation or both.

Fatty acid oxidation leads to increase in acetyl CoA level, which by inhibiting pyruvate dehydrogenase prevents further conversion of pyruvate into acetyl CoA. This results in excess pyruvate accumulation which goes into gluconeogenic pathway via lactate or alanine.

FA oxidation also increases the mitochondrial citrate concentration, which by inhibiting phosphofructokinase (key glycolytic enzyme) and intermediary reactions inhibits phosphorylation of glucose and thus preserves glucose.

THE GLUCOSE – FATTY ACID – KETONE BODY CYCLE

(Stanley, 1981)

When blood glucose (and particularly liver glycogen) concentration decreases, then fatty acids are mobilized from the adipose tissue and these are oxidized by the various tissues. Oxidation of FA specifically inhibits glucose utilization. Previously the reduced rate of mobilization and oxidation of fatty acids was thought to be due to increased blood glucose concentration, but the latest concept attributes this to an increase in the concentration of insulin. Insulin by inhibiting fatty acid mobilization and oxidation increases glucose utilization, this is the homeostatic role of insulin (Newsholme, 1977). This results in blood glucose concentration being maintained near normal level. This further allows delicate control of FA mobiliztion and oxidation and glucose utilization.

A triglyceride meal followed by injection of heparin or noradrenaline

leads to increased blood FA concentrations, decreased glucose utilization and impaired glucose tolerance. Administration of nicotinic acid (an antilipolytic agent) in human subjects decreases FA concentration and improves glucose tolerance (Stanley, 1981). Likewise inhibitors of FA oxidation (Pent-4- enoic acid), when administered to human subject, produce decrease in blood glucose level. All these are indicative of the in-vivo operation of the control mechanisms.

In the post- absorptive period the brain utilizes 120 gms. glucose daily. This much glucose in completely oxidized to water and carbon dioxide (via pathways of glycolysis, TCA cycle and respiratory chain) and represents a net loss of carbohydrates to the body. As liver glycogen can provide glucose for only 24 hours, any additional glucose must be produced by gluconeogenesis (from muscle protein breakdown) or the brain must use some alternative fuel. In prolonged starvation, the glucose requirement of the brain comes down to only 35 gms. a day while simultaneously rate of KB utilization increases (Owen et al, 1967). The brain possesses all the enzymes necessary for KB utilization and does utilize them pretty well.

The mechanism, whereby KB utilization inhibits glucose utilization in brain is likely to be similar to the one whereby FA oxidation inhibits glucose utilization in muscle. The KB oxidation acts in two ways:-

(i) It inhibits pyruvate dehydrogenase activity by increas ing concentration of acetyl CoA and the ratio acetyl CoA : CoA, thereby sending pyruvate in the gluconeogenic pathway.

(ii) It inhibits phosphofructokinase and hexokinase, by increasing concentration of citrate with a resultant fall in cerebral glucose utilization.

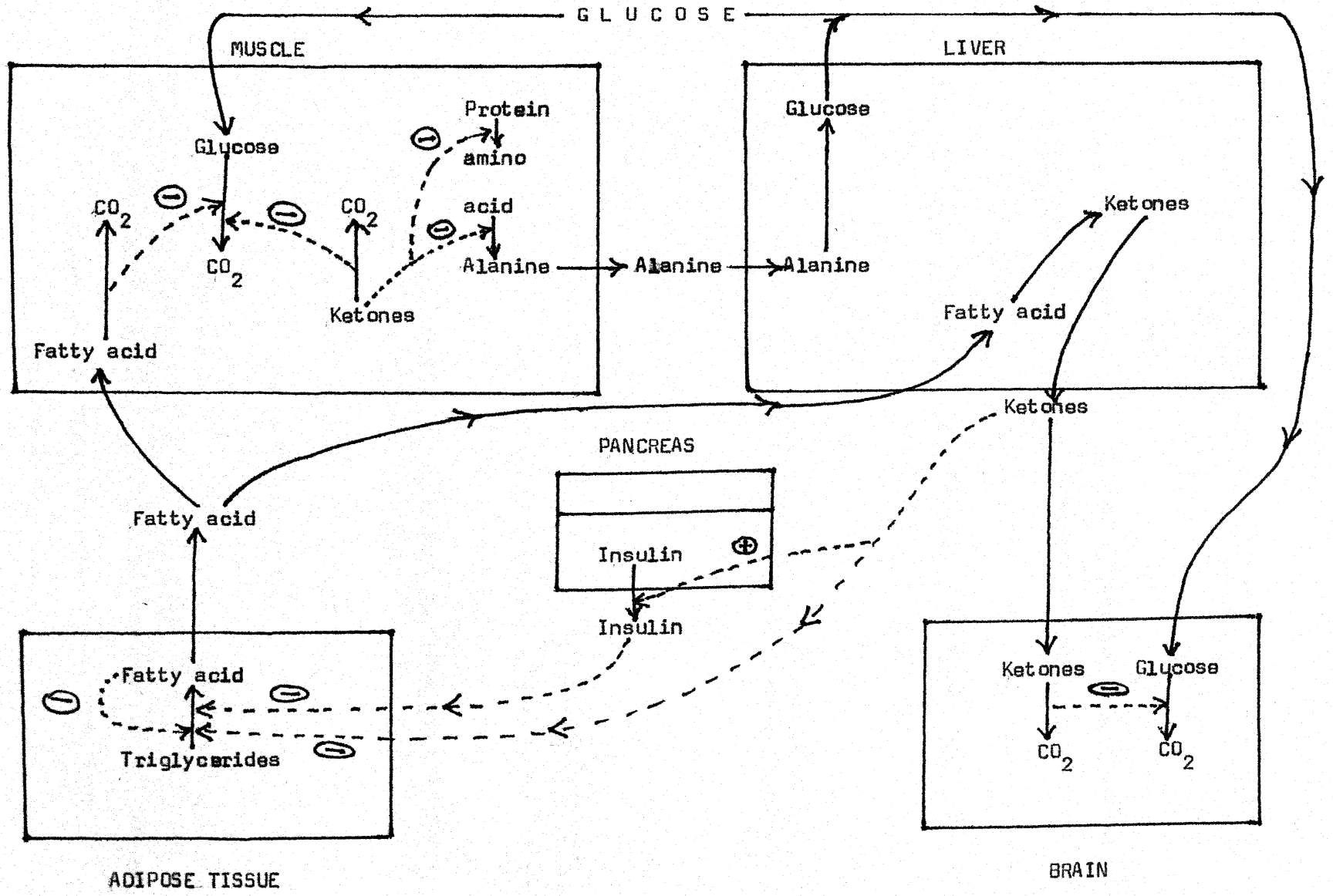

FIG. 11 - THE GLUCOSE-FATTY ACID-KETONE BODY CYCLE.

The kidney cortex uses about 34 gms. glucose daily in post-absorptive period. But during prolonged starvation, all available glucose is utilized by the anae robic tissues and brain, while kidney utilizes FA and KB. Similarly, small intestine also oxidizes FA and KB while glucose utilization is decreased. This decreased glucose utilization in small intestine is not due to citrate accumulation, but rather due to a decreased concentration of glycolytic enzymes - hexokinase, phosphofructokinase and pyruvate- kinase (Hansen & Parsons, 1978). Hence abilily of KB as alternative fuel for brain, kidney and small intestine helps in conservation of glucose.

ROLE OF KETONE BODIES IN INTEGRATING THE METABOLISM OF MUSCLE, LIVER & BRAIN

Recent studies suggest that KB directly inhibit the rate of protein degradation in muscle and the rate of alanine release in the blood. Thus infusion of alanine into patients recovering from surgery increases the plasma KB concentration and reduces urinary nitrogen excretion. Conversely, infusion of KB in starving man reduces the plasma alanine concentration and the urinary nitrogen excretion.

Possible mechanism of action is that KB increase the concentration of leucine (and other similar branched-chain amino acids) by inhibiting alpha- ketoisocaproate dehydrogenase multienzyme comples. This increased leucine concentration promotes protein synthesis by inhibiting the rate of protein degradation.

Regulation of ketogenesis - The synthesis of acetoacetate and 3-Hydroxybutyrate from fatty acids involves co-operation of the two tissues — adipose tissue (fatty acid mobilization) and liver (synthesis of ketone bodies from fatty acids).

In liver FA are first esterified to fatty acyl CoA, which is again esterified either with glucose-3- phosphate to resynthesize triacylglycerol or with carnitine to form fatty acylcarnitine. Inside mitochondria, fatty acylcarnithine is converted back to fatty acyl CoA; which undergoes beta-oxidation to form acetyl CoA. To ensure ketogenesis, fatty acyl CoA must be directed towards mitochondria; this can involve, either inhibition of triacylglycerol resynthesis, or stimulation of FA transport into mitochondria (by stimulating carnitine- acyl-transferase-I) or a combination of both. Similarly, mitochondrial acetyl CoA can enter (i) TCA cycle (CO_2 production) or (ii) HMG- CoA pathway (KB production); for ketogenasis to occur either inhibition of TCA cycle or stimulation of HMG- CoA pathway or a combination of both is necessary. The capacity of TCA cycle, does, indeed decrease in in-vivo studies; but no change in capacity of HMG- CoA pathway is observed.

Factors which integrate the mobilization of FA (from adipose tissues) and the synthesis of KB from these FA (in liver) are blood levels of insulin, glucagon and KB. Enhanced ketogenesis during starvation is due to decreased level of antilipolytic hormone insulin in presence of increased level of the ketogenic hormone glucagon.

Glucagon inhibits acetyl CoA carboxylase via cAMP and cAMP dependent protein kinase. This results in decreased synthesis of malonyl CoA which de-inhibits carnitine- acyl-transferase-I with resultant increased ketogenesis.

On the other hand high concentrations of KB stimulate secretion of insulin which directly inhibits the rate of FA mobilization from adipose tissue and increases sensitivity of this tissue to the effect of insulin (Green et al, 1979). Ketone bodies thus act as metabolic signals for activation of a sensitive feed-back control mechanism.

METABOLIC CHANGES DURING INJURY, ANAESTHESIA AND SURGERY

Body reacts to any biological insult (injury, anaesthesia or surgery) by series of changes in metabolism and hormone secretion. These changes can, conveniently, be subdivided according to the various phases:-

1. Changes caused by injury itself.
2. Modification in changes by anaesthesia.
3. Re- modification of these changes by surgical procedures superimposed on previous injury and anaesthesia.

METABOLIC CHANGES DURING INJURY- Cuthbertson (1970) demonstrated the "ebb", "flow" and "necrobiotic" phases after different injuries in man. Sometime a prehypovolumic stage precedes "ebb" phase.

"Ebb" phase may last for 2 days following injury. It is characterized by a diminished capacity for heat production and exygen consumption is reduced in environment below thermoneutral range (Temperature 28° - 32°C and Relative humitity 30% - 40%). Hyperglycemia seen is directly proportional to degree and nature of injury. Afferent impulses from damaged tissue, volume receptors (hypovolumia) and pressure receptors (hypotension) lead, via reflexes involving mesencephalic and hypothalamic centres, to increased secretion of catecholamines.

During prehypovolumic stage, the carbohydrate (glucose and its polymers glycogen and glucose phosphate) utilization is increased. Depletion of liver —— and muscle-glycogen soon causes hyperglycemia upto 4 times of previous level persisting for few hours. Surprisingly the glycogen content of brain remains the same, while that of myocardium actually increases. The glucose disposal rate (R) reduces in proportion to fall in oxygen consumption resulting from impaired thermoregulation following trauma. The concentration of insulin decreases and resistance

to insulin developes which may continue into "flow" phase. The factors implicated for insulin resistance are circulating concentration of adrenaline, pituitary growth hormone and glucocorticoids.

The "flow" phase (i.e. next several days) is characterized by raised basal metabolixm, increased heat production and increased oxygen consumption. Type and severity of injury, age, sex, previous nutrition and environmental temperature affect the increase in metabolism. Carbohydrate metabolism shows increased gluconeogenesis and is complicated by the administration of various intravenous infusions. The respiratory quotient shows a shift from carbohydrate to lipid metabolism. The rates of glucose disposal and insulin secretion may reach new peak values.

"Necrobiosis" is the terminal phase in fatal cases. All features of classical untreated shock are seen. Oxygen transport to the cells and tissues progressively deteriorates. Combination of progressive hypoxia and decreased gluconeogenesis leads to a terminal hypoglycemia. Theanaerobic metabolism of glucose leads to pyruvate accumulation both in cells and blood. The lactate/pyruvate ratio also rises.

In a nutshell, mild injury leads to very little metabolic changes, but severe, extensive injuries (multiple fractures, severe burns) are notorious. The extent of changes in such situations may be upto 30% - 40%. The plasma concentration of FFA is sharply increased and disposal rate of plasma chylomicrons or infused fat emulsions is accelerated. Blood glucose concentration is universally raised because increased sympathetic activity nullifies the normal negative feedback control of glucagon.

METABOLIC AND ENDOCRINAL CHANGES DURING SURGICAL PROCEDURES- Surgical procedures evoke, an endocrine response (substrates mobilization, a shift towards catabolism, negative nitrogen balance and salt & water retention) in direct proportion to the magnitude of surgical trauma; Thus intra- abdominal procedures evoke a much greater response than the body surface surgery (Clarke, 1970; Clarke et al, 1970) and cardiac surgery with cardiopulmonary bypass induces profound hormonal and biochemical changes (Stanley et al, 1979).

The initial response to surgical trauma is an increased concentration of catabolic hormones (catecholamines, glucagon, cortisol) with concommitantly decreased circulating concentrations of anabolic hormones (insulin & testosterone). Nistrup Madsen and collegues (1978) demonstrated good correlation between changes in plasma adrenaline and cAMP values. Plasma level of cAMP (a common intracellular second messanger for beta- adrenergic agonists) rises proportionate to the severity of surgery (Nistrup Madsen et al, 1976).

Catecholamines - The more specific and sensitive radioenzymatic assay techniques have resulted in conflicting opinions on the role of circulating catecholamines as mediators of the metabolic response to surgery.

Abdominal surgery increases both adrenaline and noradrenaline values (Halter et al, 1977), while pelvic surgery results in a increase of adrenaline alone (Nistrup Madsen et al, 1978; Engquist et al, 1980). Interestingly, maximum change in plasma adrenaline value was found after reversal of anaesthesia in both types of surgery. Silverberg et al, (1978) and Clutter et al (1980) attributed changes in heart rate, arterial blood pressure, blood glucose, lactate and glycerol levels to increased adrenaline concentration rather than to that of noradrenaline.

Alpha-adrenergic blockade with phentolamine (Allison et al, 1969) and beta-adrenergic blockade with propranolol (Cooper et al, 1980) do not significantly alter the overall metabolic responses. The observation made by Butler et al (1977) that the ideal method of assessing the individual catecholamine response to surgery has yet to be defined, is undoubtedly still valid.

Cortisol and ACTH - Depending upon the severity of surgery, the plasma cortisol level rapidly increases and remains elevated for a variable time after operation (Gordon et al, 1973). The increased cortisol production is secondary to increased ACTH secretion, but the increase in ACTH level is far more than is necessary to produce a maximal adrenocortical response (Thoren, 1974). The normal pituitary- adrenocortical feedback mechanism is no longer effective. ACTH administration during surgery does not increase plasma cortisol any further, while corticosteroid administration fails to abolish the ACTH - cortisol response in postoperative period (Thoren, 1974).

Large doses of ACTH or hydrocortisone in normal subjects resemble many features of surgery (hyperglycemia, protein degradation, sodium and water retention, potassium loss), However this increased cortisol concentration has a " permissive " effect rather than a direct causative role according to present concepts. Thus, severe hyperglycemia of thoraco- abdominal surgery can be markedly decreased in the presence of a normal adrenocortical response (Bromage et al, 1971) and adrenalectamized patients maintained on constant doses of glucocorticoids develop a negative nitrogen balance after operation (Johnstone, 1964).

Growth Hormone - Has mixed anabolic and catabolic effects — promotes protein synthesis, is lipolytic and in high concentrations, is diabetogenic (Oyama et al, 1970). Its level increases during surgery (Hall et al, 1978), but does not remain elevated post-operatively even after extensive operations like cardiac surgery (Brandt et al, 1978). In non-stress states growth hormone secretion is stimulated by hypoglycemia, while glucose administration depresses the same. Growth hormone plays a relatively minor role, because a normal metabolic response to surgery is seen in hypophysectomized patients maintained on steroid replacement therapy (Thoren, 1974).

Glucagon - Increased plasma glucagon concentrations occur in burns and major injuries (Lindsey et al, 1974) and also in a wide variety of major surgical procedures (Russell et al, 1975), Increased plasma glucagon level upto 4 days, is seen during gastric surgery or surgery with complications. However foster and collegues (1980) observed normal plasma glucagon level within 48 hours after major abdominal surgery.

Control of glucagon secretion is multifactorial (Alberti et al, 1977). A non-stress induced hyperglycemia produces fall in glucagon level, but this mechanism is not operative in stress-induced hyperglycemia (Unger et al, 1962).

Insulin - Plasma insulin level falls during and just after surgery inspite of co-existing hyperglycemia but returns to normal or above-normal values in late post-operative period (Russell et al, 1975).

The relationship between insulin and glucagon secretion is complex. Initially insulin level falls, while glucagon level increases, but later in post-operative period both are increased. Pre-dominance of

alpha-adrenergic sympathetic activity results in inhibition of insulin secretion (Allison, 1971). Patients receiving beta-blocking drugs show similar fall in insulin level (Cooper et al, 1980).

Most probably the metabolic response to surgery is the result of the increased activity of all the catabolic hormones in the presence of a reduced activity of the key anabolic hormone —— insulin.

PROTEIN METABOLISM - There is an initial decrease in protein synthesis in muscles followed by increased protein catabolism. De-amination of resultant amino acid flux in the liver results in increased urea production and urinary nitrogen excretion. The duration and magnitude of this nitrogen loss is related to severity of surgery and nutritional status of patient (Fleck, 1980). A man of average built may lose upto 0.5 kg. lean tissue mass per day for 4 - 5 days after major abdominal operation, this much loss in severely debilitated patients indicates poor prognosis (Johnstone, 1964).

Alanine derived from muscle protein breakdown, is taken up repidly during surgery to ensure sufficient hepatic gluconeogenesis (Elia et al, 1980).

CARBOHYDRATE METABOLISM - Hyperglycemia is proportionate to severity of surgery and values upto 10 mmol/litre may be found during cardiac surgery. This may cause glycosuria (Brandt et al, 1978). Normal neuro-humoral regulation is no longer effective, insulin supression is seen early in the surgery. Aarimaa et al, (1974), by using serial intravenous glucose tolerance test, showed decreased glucose utilization and resistance to insulin during surgery. Relative contribution of hepatic glycogenolysis and gluconeogenesis towards hyperglycemia are controversial (Cooper et al, 1980 ; Richards, 1980).

FAT METABOLISM - Increased FFA mobilization may account for reduced glucose utilization, but FFA concentration during surgery show little changes (Hall et al, 1978; Kehlet et al, 1979). Heparin administration during surgery causes a large and immediate increase in plasma FFA values due to stimulation of lipoprotein lipase enzyme.

For ketone bodies, values of 250 mmol/litre after cardiac surgery (Brandt et al, 1978) and 2 mmol/litre after hysterectomy (Kehlet et al, 1979) were seen. This wide variation in ketone bodies response to surgery is possibly similar to that seen during starvation (Rich et al, 1979).

ACTIVATION OF RESPONSE - Increase in afferent somatic and autonomic nerve fibre activity is important in initiating the response to surgery (Wilmore et al, 1976), because analgesia per se does not prevent the hormonal changes (Bromage et al, 1971).

The existance of various wound hormones (Prostaglandins, serotonin, acetylcholine and amino acids released by damaged tissue) is somewhat doubtful (Egdahl, 1959), but still may have some role in severe burns and trauma (Wilmore et al, 1976). Haemorrhage, starvation and dehydration all play some role. Premedication and sleep pattern of previous night influence the plasma cortisol values (Oyama, 1973). Infection, prolonged bed rest, hypoxaemia and the biological day-night rhythm also affect this response to surgery.

ENDOCRINE AND METABOLIC CHANGES WITH ANAESTHESIA -

" The most striking, the most constant and one of the most consequential disturbances of metabolism during anaesthesia is the rise in the glucose and lactic acid content of circulating blood"

(Harris, 1951).

In recent years, this view has not been confirmed in man and in the absence of surgery, anaesthesia with various anaesthetic agents has not been shown to cause a significant increase in the blood sugar level (a parameter most commonly studied by the various workers).

Even deep surgical anaesthesia or profound analgesia can only suppress the afferent impulses (pain etc.) which continue to flow into cerebral cortex along primary pathways and excite cells in appropriate sensory areas.

All anaesthetic agents, as a rule, inhibit and interfere with cellular respiration and enzymatic processes. They affect hepatic as well as myocardial metabolism but cerebral metabolism is relatively unaffected.

Anaesthetic agents affect carbohydrate metabolism (Variable hyperglycaemia, glycosuria, impaired glucose tolerance); Increased concentration of catabolic hormones with decreased concentration of anabolic hormones; Lipid metabolism (lipolysis with little change in plasma FFA, glycerol and ketone bodies levels); protein metabolism (protein sparing effect with variable nitrogen balance and urinary nitrogen-urea excretion).

Spinal anaesthesia without surgery reduces catecholamine levels. Barbiturates interfere with oxidation of Nicotinamide Adenine dinucleotide

dehydrogenase (NADH). Thiopentone-Nitrous oxide anaesthesia with or without relaxants causes little hyperglycemia. First dose of Propanidid causes no hyperglycemia, but subsequent doses do so upto variable extent.

DI - ETHYL ETHER - This is unique among the inhalational agents in causing a liberation of glucogenic hormones other than catecholamines, as well as raising the blood sugar, in producing lactic acidosis and in failing to lower the elevated FFA level (J.C. Stanley, 1981).

It induces hyperglycemia (Cullingford, 1966). Oyama and Takazawa (1971) recorded a mean rise of 7 mg/dl in blood glucose over a period of 45 minutes of anaesthesia with ether.

I - Sympatho- adrenal Response - Ether increases sympathoadrenal activity producing significant rise in the concentration of circulating adrenaline and noradrenaline (Elliot et al, 1968; Black et al, 1969; Singhal et al, 1982). Studies by Miller and Biscoe (1966) show that ether increases the postganglionic sympathetic discharge.

Black and his collegues (1969) suggested that this increase in sympathoadrenal activity is an attempt to offset the depressant effects of anaesthetic agent on cardiovascular system.

The hyperglycemia is mainly due to hepatic glycogenolysis (Annamunthodo et al, 1958), is less pronounced in man with liver disease and does not occur in hepatactomized animals. Total sympathetic blockade prevents it (Brewster et al, 1952).

Griffiths (1953) attributed this hyperglycemic response and hepatic glycogenolysis to two factors " the direct action of a hepatotoxin (the anaesthetic agent) on the liver cells" and "sympathetic stimulation acting through sympatho- adrenal mechanism". But Cullingford (1966) contended that ether anaesthesia in absence of surgical stimulus seldom produces hyperglycemia. A logical

explanation is that, ether anaesthesia increases level of noredrenaline alone in man (Price, 1957) in contrast to both adrenaline and noradrenaline in animals (Brewster et al, 1952; Richardson et al, 1957). Since noradrenaline is largely devoid of metabolic effects the difference between animal and human response to ether is obvious.

The sympathetic stimulation caused by ether produces a significant rise in the blood FFA level by increasing the rate of lipolysis (Henneman et al, 1961; Oyama et al, 1971). Singhal and collegues (1979) also noted a significant rise in the blood FFA level during ether anaesthesia. But Cooperman (1970) observed no significant rise in blood FFA level with this agent.

II- Adreno- cortical Response - Ether is the strongest stimulant of adrenocortical activity among the various anaesthetic agents (Hammond et al, 1958; Vandam and Moore, 1960). Neither a deep plane of anaesthesia nor a duration of over one hour is necessary to produce significant adreno- cortical response (Oyama et al, 1968). Some workers reported distinct rises in plasma ACTH and cortisol levels following ether anaesthesia. In fact the cortisol response is largely due to surgical stress. The corticosteroids are somehow responsible for insulin resistance seen in patients during stress.

III- Direct response - Ether anaesthesia has a direct effect on carbohydrate metabolism (Bunker, 1962), possibly by interfering with cellular transfer of glucose thereby impeding phosphorylation and subsequent metabolism of glucose. It also inhibits electron transfer at or near the NADH dehydrogenase locus, (Cohen et al, 1972).

Ether causes marked rise in plasma catecholamines and cAMP levels. The catecholamine- induced lipolysis is believed to be

mediated by a cAMP system (Sutherland et al, 1968). Therefore during increased sympathetic nervous activity, plasma FFA levels rise.

Cooperman (1970) in man observed no significant change in FFA level. The marked hyperglycemia seen with ether anaesthesia may cause marked inhibition of FFA release from adipose cells and this may account for no apparent rise in FFA level.

TRI- CHLORO- ETHYLENE - The analgesic concentrations (1%) of this agent cause universal unawareness in the patients (Prior, 1972; Kumar and Saxena, 1977). The acid- base parameters remain remarkably steady and comparable with the control cases (Dobkin and Bayliss, 1962; Kohli, Punnoose, Srihari and Gode, 1977).

I- Sympatho- Adrenal Response- Remarkable cardiovascular stability is seen with low concentrations of this agent in man and animals (Dobkin et al, 1962). Heart rate and arterial blood pressure remain very much stable and no cardiac arrhythmia is seen with such low concentrations (Dobkin et al, 1962; Holmes et al, 1963; Leatherdale, 1966; Kohli, Punnoose, Srihari and Gode, 1977). On the contrary, hypotensive pressures (as low as 80 mm.Hg.) with or without bradycardia due to vagal stimulation, are sometimes seen (Holmes et al, 1963; Prior et al, 1965).

There is no alteration in plasma noradrenaline levels during trichloroethylene anaesthesia (Elliot et al, 1968). Adrenaline is responsible for the cardiac arrhythmias during this anaesthesia in man (Lloyd- Williams et al, 1943; Barnes et al, 1944; Richards et al, 1962) but all such arrhythmias dissappeared when the inhaled concentration of trichloroethylene is reduced and the hypercarbia is corrected (Malhotra et al, 1977).

It causes hyperglycemia and lactic acidosis. The mechanism of this hyperglycemia is not well- understood (Sikh, 1966). The possible explanations are that this agent enhances breakdown of tissue glycogen and a diminished peripheral glucose utilization due to depressed metabolism (Krantz and Carr, 1965) and by increasing the level of circulating catecholamines (Dobkin et al, 1962; Dixit, 1972; Lakshmi et al, 1973; Dev et al, 1977; Singh et al, 1977).

It stimulates the sympathetic receptors and this causes increased level of circulating catecholamines, which results in activation of adenyl cyclase- cAMP- lipoprotein lipase system with resultant increased lipolysis from the adipose tissue and increased level of blood FFA.

II- Direct Response - Olson and Spencer (1968) observed an increase in the mitochondrial volume change caused by ATP or ADP, an increase in ATP hydrolysis and an increase in mitochondrial respiration.

HALOTHANE:-

I - Sympatho- Adrenal Response - Halothane anaesthesia is associated with a small and insignificant rise in plasma catecholamine level in absence of surgery (Black and McArdle, 1962; Elliot et al, 1968). Singhal et al (1982) recorded a slight rise in plasma noradrenaline level (mean preanaesthetic value 3.3 μgm./litre, mean value after induction but before start of surgery 3.7 μgm./litre), while Roizen et al (1974) and Halter et al (1977) saw a fall in plasma catecholamines.

A combination of central autonomic paresis, ganglionic blockade and supression of peripherel action of the sympathetic

transmitter tends to prevent the rise of plasma noradrenaline during halothane anaesthesia (Price et al, 1963; Price et al, 1966; Miller and Biscoe, 1966). Suppression of baroceptors allows halothane to exert its direct depressant effects on heart and peripheral vasculature, without the usual compansatory mechanism being brought into play (Price et al, 1963).

Reisener and Lippmann (1975) observed cardiac dysrhythmia with subcutaneous infiltration of adrenaline (1:100000 — 1:300000) during halothane anaesthesia, but Gilani et al(1982) found no untoward cadiovascular effect. This also suggests peripheral sympathetic blockade during halothane anaesthesia.

Reports on effects of halothane on blood glucose and FFA are controversial. Allison et al(1969), Merin et al(1971), Oyama et al (1971), Lakshmi et al (1973), Makelainen (1974) and Gupta, Jain & Pandey (1982) noticed rise in blood glucose. But Hunter (1959), Tarhan et al (1971) and Yoshimura et al (1971) observed no such change. Insulin suppression was also seen with halothane (Allison et al, 1969; Aynsley- Green et al, 1973).

Like wise, plasma FFA level recorded a rise in serieses of Cooperman (1970), Merin et al (1971), Makelainen (1974) and Gupta, Jain & Pandey (1982); but not in those of Oyama et al (1971) and Tarhan et al (1971).

II- Direct Response - Halothane has been known to inhibit the glycolytic enzymes (Schweizer et al, 1969) and the cellular uptake of glucose (Green, 1965; Ngai, 1972). Halothane also blocks electron transfer between NADH & Flavoproteins and depresses oxygen uptake by the cells. It is an uncoupler of oxidative phosphorylation (Miller and Hunter, 1970, 1971). It also depresses FFA uptake by the myocardium

(Merin et al, 1971).

Makelainen (1974) attributed the rise in plasma FFA following halothane anaesthesia to stimulation of beta-adrenergic receptors leading to an increased lipolysis via the adenyl cyclase- cAMP-lipase system. Halothane also depresses FFA uptake by myocardium. Fatty acid administration leads to a decrease in the halothane inhibition of oxygen consumption, gluconeogenesis and urea synthesis.

Thus it can be seen that the influence of modern inhalation and intravenous agents, on hormone secretion and metabolism is small as compared to that of surgical stimulation provided that hypoxaemia, acidosis and hypothermia are avoided (Traynor et al, 1981). Indeed halothane may even be beneficial as it has been shown to reduce adrenaline secretion in-vitro and in-vivo (Roizen et al, 1974; Halter et al, 1977).

The neuro-endocrine response to trauma appears to have evolved to assist survival in a more primitive environment by providing appropriate substrates to maintain vital functions. However in modern anaesthetic and surgical practice, where severe physiological disturbances are prevented or rapidly treated with prompt adminstration of suitable substrates, any benefits of this response are no longer apparent. The aim for the future must be the safe prevention of surgically induced, adverse hormonal and metabolic changes to ensure well-being of the patients (Traynor and Hall, 1981).

MATERIAL & METHODS

MATERIAL AND METHODS

SUBJECT OF STUDY:-

The study was conducted on a series of 90 patients of either sex ranging between 15 - 60 years of age, admitted at the M.L.B. Medical College Hospital, Jhansi for elective operation from various surgical specialities. The actual operative duration lasted from 45 to 90 minutes (excluding the duration prior to commencement of surgery itself). The patients selected were from A.S.A. Grade I or II.

SELECTION OF PATIENTS:-

Only patients, fulfilling the following criteria, were selected for the present study:-

1. Patients were between 15 - 60 years of age.
2. Patients were of either sex (Male/Female).
3. The history of the patient did not suggest any disorder, other than that for which the patient was being kept for surgery.
4. On detailed clinical examination of the patient, there was no evidence suggestive of some systemic, metabolic, endocrinal, hepatic, renal, cardivascular or neurological disorder.
5. The anticipated duration of surgery was within 45 - 90 minutes.
6. The patient did not regularly take any drug likely to influence the levels of sugar or FFA in the blood (particularly hypoglycaemics, hormones, corticosteroids, alpha- and beta- blocking drugs and drugs causing hyper- or hypocholesterolaemia), atleast not within 15 days preceding the operation.
7. The patient did not receive any dextrose-water, dextrose-saline, plasma-expander solution or blood transfusion during the 24 hours preceding the operation.

8. The patient, (if subjected to any previous anaesthetic-surgical procedure), did not show any unusual response.

INVESTIGATIONS:-

Every patient was investigated for the following:-

1. Total leucocyte count.
2. Differential leucocyte count.
3. Erythrocyte Sedimentation Rate.
4. Urine for sugar and albumin.
5. Urine for microscopic examination.
6. Blood grouping and cross-matching (wherever indicated).
7. Blood urea (if indicated).
8. Serum cholesterol (wherever desired).
9. Liver function tests (wherever indicated).
10. Plain X-ray chest (P-A view) (where desired).
11. Plain X-ray abdomen (P-A view) (wherever required).
12. Intravenous pyelography (where indicated).
13. Blood sugar in the serial blood samples.
14. Plasma free fatty acids (FFA) in the serial blood samples.

PREMEDICATION AND PREPARATION OF THE PATIENTS:-

The anaesthetic and operative procedures were carefully explained to all patients. They were properly assured in order to allay any anxiety or apprehension, they might had entertained. Special care was taken to avoid any undue alarm on the part of patients.

All the patients were given lorazepam 2 - 4 mg orally in the night preceding the operation. There after, they were allowed nothing by mouth for about 5 - 7 hours prior to operation.

All the patients were given injection atropine 0.65 mg

intramuscularly 45 minutes before the induction. No other premedication was given.

ANAESTHESIA:-

Anaesthesia was administered to all the patients in following way:-

(A) INDUCTION:- Pre-oxygenation of the patient for 5 minutes followed by the sleep dose of 2.5% solution of Thiopentone sodium and injection Succinylcholine 1 mg/kg were given. After intermittent positive pressure ventilation of 1 - 2 minutes all the patients were intubated either oroendotracheally or nasoendotracheally.

(B) MAINTENANCE:- Patients were maintained on any one of the following:-

I	II	III
Oxygen + N_2O	Oxygen + N_2O	Oxygen + N_2O
+	+	+
Di-Ethyl Ether	Trichloroethylene	Halothane
(6% - 10%)	(0.5% - 1.0%)	(0.5% - 1.0%)

An anaesthetic gas mixture of oxygen and nitrous oxide in the ratio of 40 : 60 with a total flow of 6 - 8 litres/minute (equal to the minute volume of the patient) along with the particuler inhalational anaesthetic agent was adminstered to the patient, using a Magill's semi-closed circuit. Sub-apnoeic doses of non-depolariser muscle relaxant were used, if needed.

Although no blood gas analysis was done, every care was taken to avoid hypoxia, hypercarbia, excessive tachycardia or excessive tachypnoea, Hyperventilation was also avoided. Similarly adequate analgesia and anaesthesia was maintained through

out the whole procedure.

(C) REVERSAL:- At the end ofoperation, the patients were reversed from anaesthesia by gradually decreasing the concentration of inhalational anaesthetic and Nitrous oxide, while increasing that of Oxygen. Then patients were allowed to breathe 100% Oxygen for 5 minutes. Patients were shifted to Post-operative ward, when they could maintain a proper airway on their own and the protective reflexes had returned.

INTRAVENOUS FLUID ADMINISTRATION DURING WHOLE PROCEDURE:-

Patients were transfused only with 0.9% physiological saline (Sodium Chloride) solution. 5% dextrose-water or dextrose-saline solution were avoided, because they may alter the sugar or FFA level in the blood. The solution was infused at the minimum rate and a maximum of 1000 ml fluid was infused.

WITHDRAWAL OF BLOOD SAMPLES:-

Serial blood samples were taken for the estimation of sugar and FFA in the blood. Samples were withdrawn from the ante-cubital vein (or some suitable vein)by a wide bore needle, under strict aseptic precautions, as under:-

(a) First sample was taken 45 minutes after premedication and just before induction of anaesthesia.

(b) Second to fifth samples were taken after induction of anaesthesia at 5, 15, 30 and 45 minutes respectively.

(c) Sixth and seventh samples were taken after start of surgery at 20 and 45 minutes respectively.

The samples were stored at $0^{\circ}C$ and analysed for blood sugar and FFA at the earliest possible time.

The mean values of the first samples (taken just before the

induction of anaesthesia) served as controls, with which the subsequent serial mean values of these parameters in each group were compared statistically.

DETERMINATION OF BLOOD SUGAR LEVELS

Modified Folin Wu's technique was adopted which is most widely used upto the present time, especially in hospital laboratories. The estimations were done at the earliest possible time to overcome the error which occurs due to reduction of blood glucose on storage.

The basic principle of this technique is — precipitation of blood proteins, reduction of alkaline cupric sulfate to cuprous oxide, and estimation of the amount of such reduction colorimetrically.

Reagents:-

1. Sodium tungstate 10% - made by dissolving 10 gms. of $Na_2 WO_4 . 2H_2O$ in water and solution was made to 100 ml.
2. Sulphuric acid 2/3 N. (o.66 N).
3. Alkaline copper sulfate - pure anhydrous sodium biocarbonate 40 gm. was dissolved in 400 ml. water in a litre flask. To this 7.5 gms. of tartaric acid was added and when the latter had dissolved, 4.5 gms of crystallised copper sulfate was added to it. The solution was mixed and the volume was made upto one litre.
4. Phosphomolybdic acid - Molybdic acid 35 gms. and sodium tungstate 5.0 gms. were placed in a 500 ml. beaker and to it 200 ml. of 10% sodium hydroxide was added which was followed by addition of 200 ml. of water. This solution was boiled for about 30 minutes to remove ammonia present in the molybdic acid (Volume was reduced to about 350 ml.) The solution was cooled and then 125 ml. of 85% phosphoric acid was added and the solution was diluted to 500 ml.

5. Standard glucose solution :-

Stock : 1% solution of dextrose in a 0.25% benzoic acid was made by dissolving 10 mg. of anhydrous dextrose per ml. of 0.25% benzoic acid.

Working solution : 10 ml. of stock solution was diluted to 100 ml. with 0.25% benzoic acid (1 mg/ml.).

Procedure :

Estimations were carried out in duplicates by taking 0.2 ml. blood along with blank and standard working glucose solution (1 mg = 1 ml.). 3.2 ml. of glass-distilled water was taken in a test-tube to which 0.2 ml. blood was added. To this 0.3 ml. sodium tungstate (10%) and 0.3 ml. sulfuric acid (2/3 N) was added (precipitation of blood proteins takes place). This solution was allowed to stand for about 20 minutes, was then mixed well and centrifuged for 10 minutes. 1 ml. of the supernatant was taken in another test-tube and in case of standard and blank, 1 ml. working standard glucose solution and 1 ml. distilled water respectively were taken and 1 ml. alkaline copper sulfate was added in each tube (Reduction of alkaline cupric sulfate to cuprous oxide takes place). Then the tubes were kept in boiling water for six minutes. 1 ml. phosphomolybdic acid was added in each tube and the tubes were kept again in boiling water for two minutes. To this, 9.5 ml. of glass distilled water was added to make the total volume to 12.5 ml. in each tube. The optical density was measured using blue filter in a colorimeter.

Calculations :

$$\text{Blood sugar in mg/dl} = \frac{\text{Readings of the unknown (test)}}{\text{Readings of the standard}} \times 100$$

(In each analysis, two standard solutions were treated simultaneously to reduce the error.)

DETERMINATION OF FREE FATTY ACIDS IN SERUM

Millian Novak's technique (1965) was employed for the estimation of free fatty acid in serum. The basic principle of this technique is — extraction of free fatty acid from the serum, esterification of them by the help of cobalt reagent and then their estimation colorimetrically with the help of an indicator.

Reagents :

COBALT REAGENT :

Solution A :-

Cobalt nitrate-acetic acid - potassium sulfate, was prepared by adding to a solution of K_2SO_4 (saturated while boiling, stored in contact with excess crystals, and filtered before use), 6 gms. of $Co(NO_3)_2 \cdot 6H_2O$ and 0.8 ml. of acetic acid to give a total volume of 100 ml. at 37°C.

Solution B :- a standard Na_2SO_4 solution, was prepared by adding sodium sulphate to boiling water, kept at 37°C overnight.

Preparation of cobalt reagent - Triethanolamine, 1.35 volume was made upto 10 volumes with solution A. Solution B, 7 volumes was added and the mixture was shaken. This reagent was not stable and was prepared fresh for every series of analyses. Solution A and B were kept at 37°C.

INDICATOR :

Stock solution : 0.4% alpha- nitroso- beta-naphthol in 96% ethanol was prepared by dissolving 0.4 gms. of it in 100 ml. of 96% ethanol. This stock solution 4 ml. was diluted with 46 ml. ethanol before use.

DOLE'S EXTRACTION MIXTURE :

This mixture was prepared by mixing isopropyl alcohol 40 parts, heptane 10 parts, and 1.0 N H_2SO_4 1 part (all solvents redistilled).

CHLOROFORM - HEPTANE: 5 : 1 (V/V) was made up using redistilled chloroform and heptane.

STANDARD PALMITIC ACID SOLUTION (0.05 M): This was prepared by dissloving palmitic acid 1.3 gms. in Dole's extraction mixture 100 ml. and was stored at 0.^{o}C.

PROCEDURE : Estimations were carried out in duplicates along with blank and palmitic acid standard.

To 2.5 ml. of Dole's extraction mixture in one of the glass - stoppered tube, 1 ml. serum was added. The liquids were mixed by vibration, care being taken not to allow them to reach the stopper. The test tubes were cooled for 10 minutes in a bath of melting ice. To this 3 ml. of Heptane was added followed by 4 ml. of glass-distilled water. The contents of the tube were then thoroughly mixed. After the phases had seperated, 2 ml. was drawn from the upper heptane phase and transferred to another stoppered centrifuge tube. 4 ml. of Chloroform-Heptane was added to this tube followed by 5 ml. of freshly prepared cobalt reagent and the solution was thoroughly mixed for 3 minutes. The mixture was centrifuged for 15 minutes at 2500 rpm and 4 ml. of the upper chloroform-heptane phase was transferred to a test tube containing pinch of anhydrous sodium sulfate. 3 ml. aliquot of the above dehydrated chloroform-heptane mixture was transferred to a test tube containing 3.5 ml. of the indicator solution — alpha-nitroso-beta-nephthol. The samples were treated simultaneously with the standard solution and blank.

Values were read 30 minutes later at 500 millimicrons in a spectrophotometer.

CALCULATIONS:

Standard solution : 1.3 gms. of palmitic acid ($C_{15}H_{31}COO_4$) per 100 ml. Dole's extraction mixture or 5.07 mEq/litre.

$$\text{FFA in mEq/litre} = \frac{\text{Reading of Unknown (test) solution}}{\text{Reading of standard solution}} \times 5.07$$

In each analysis, two standard solutions were treated simultaneously to reduce the error.

In general, free fatty acid and blood sugar determinations were performed on each specimen; however to test reproducibility, triplicate determinations were performed at intervals throughout the study.

OBSERVATIONS

OBSERVATIONS

For elimination of repitition, careful analysis and a technical yet simple interpretation thereof, the various raw data and observations were presented in tabulated forms as under:-

TABLE - 1

Showing distribution of patients according to inhalational agent given and the sex

Group	Inhalational agent	Total cases		Male patients		Female Patients	
		No.	(%)	No.	(%)	No.	(%)
I	Ether	30	(33.3)	18	(60.0)	12	(40.0)
II	Trichloroethylene	30	(33.3)	17	(56.7)	13	(43.3)
III	Halothane	30	(33.3)	19	(63.3)	11	(36.7)

The 90 patients studied were divided into 3 groups of 30 each according to the inhalational agent used. the male : female ratio in each group was approximately 3 : 2.

TABLE - 2

Showing age and weight distribution according to the sex of patients

Group		Age (years)		Weight (kg.)	
		Male	Female	Male	Female
I (Ether)	Mean	32.50	29.42	51.50	42.33
	S.D. ±	11.17	10.97	4.44	8.73
II (Trilene)	Mean	28.71	35.46	52.29	43.54
	S.D. ±	11.43	10.63	6.00	5.72
III (Halothane)	Mean	32.95	37.36	50.94	45.64
	S.D. ±	11.96	8.20	5.63	- 6.62

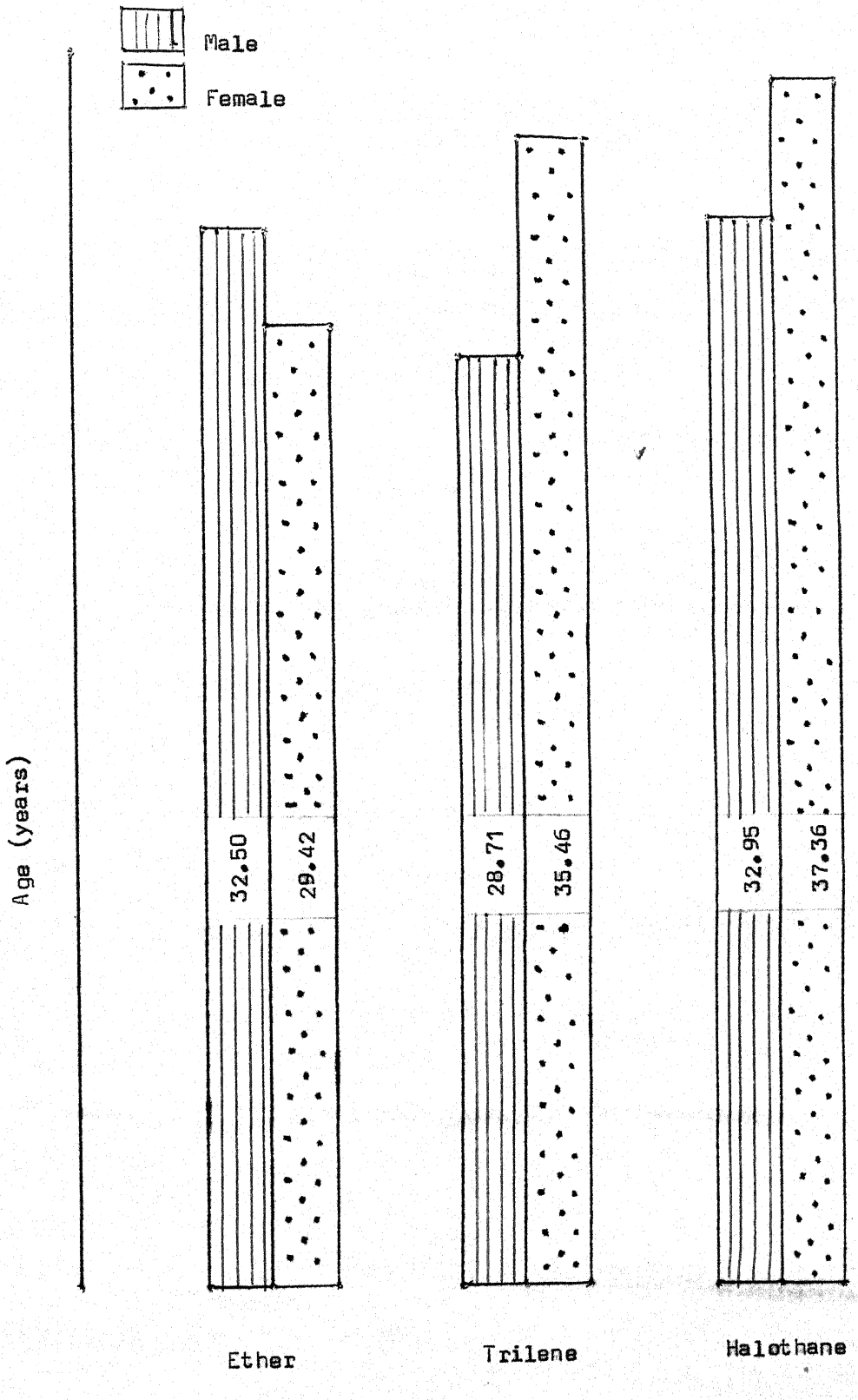

Fig. 12 - Showing mean ages of patients in the various groups.

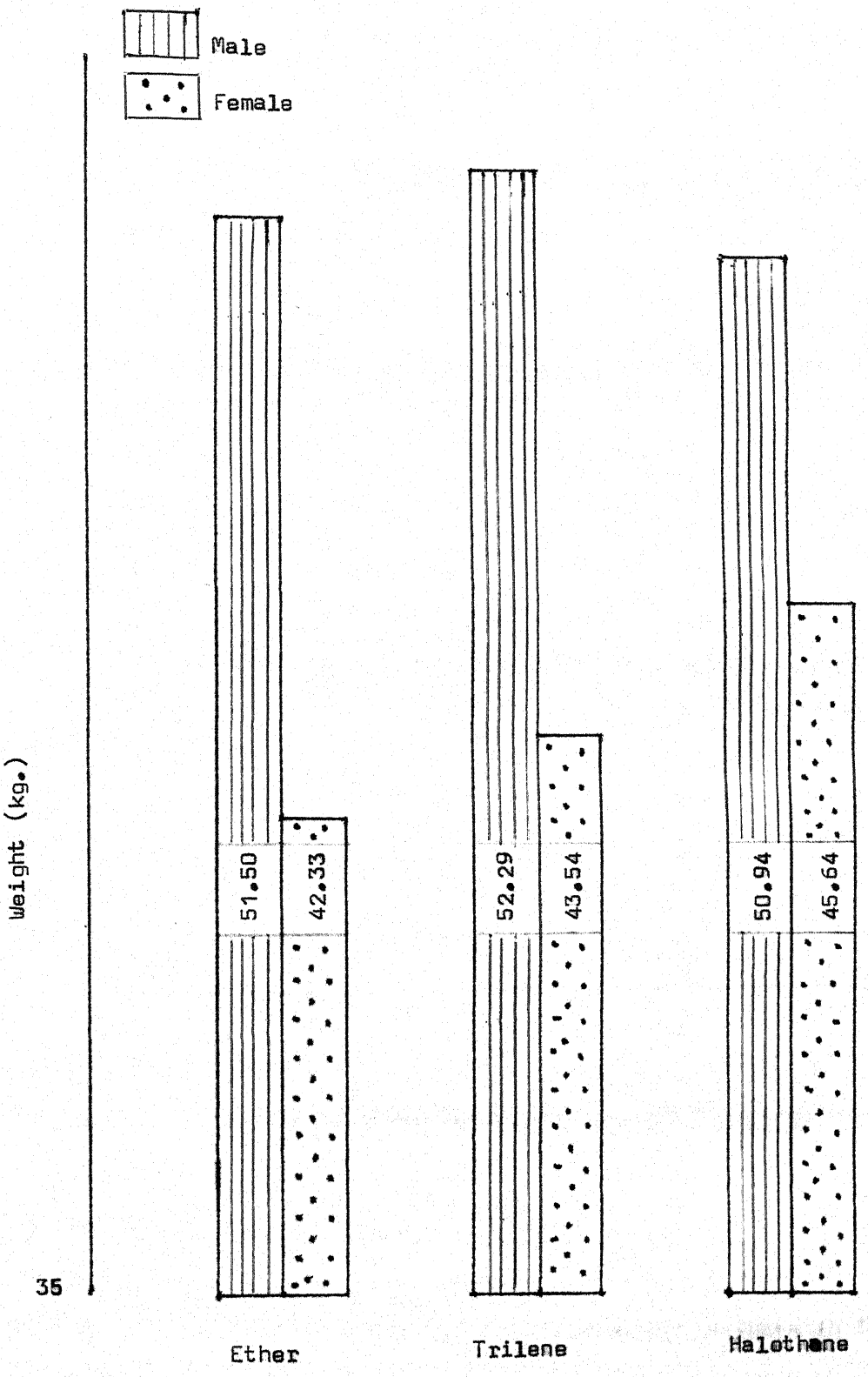

Fig.13- Showing mean weights of patients in the various groups.

In group I, II and III the mean ages of male patients were 32.50 ± 11.17, 28.71±11.43 and 32.95± 11.96 years respectively while the female patients averaged 29.42±10.97, 35.46±10.63 and 37.36±8.20 years. The mean weights of male patients in group I, II and III were 51.50±4.44, 52.29±6.00 and 50.94±5.63 kg. respectively while those of female patients were 42.33±8.73, 43.54±5.72 and 45.64±6.62 kg. respectively.

The ages (i.e. mean ages) of patients show some difference from one another, but the mean weights for patients were similar in all the three groups.

TABLE - 3

Showing number of cases according to American Society of Anaesthesiologists (ASA) physical status in various groups

Group	ASA Grade I		ASA Grade II	
	No.	(%)	No.	(%)
I (Ether)	20	(66.67)	10	(33.33)
II (Trilene)	19	(63.33)	11	(36.67)
III (Halothane)	19	(63.33)	11	(36.67)

The ratio between the numbers of patients in ASA physical status I & II was approximately 2:1 for all the three groups.

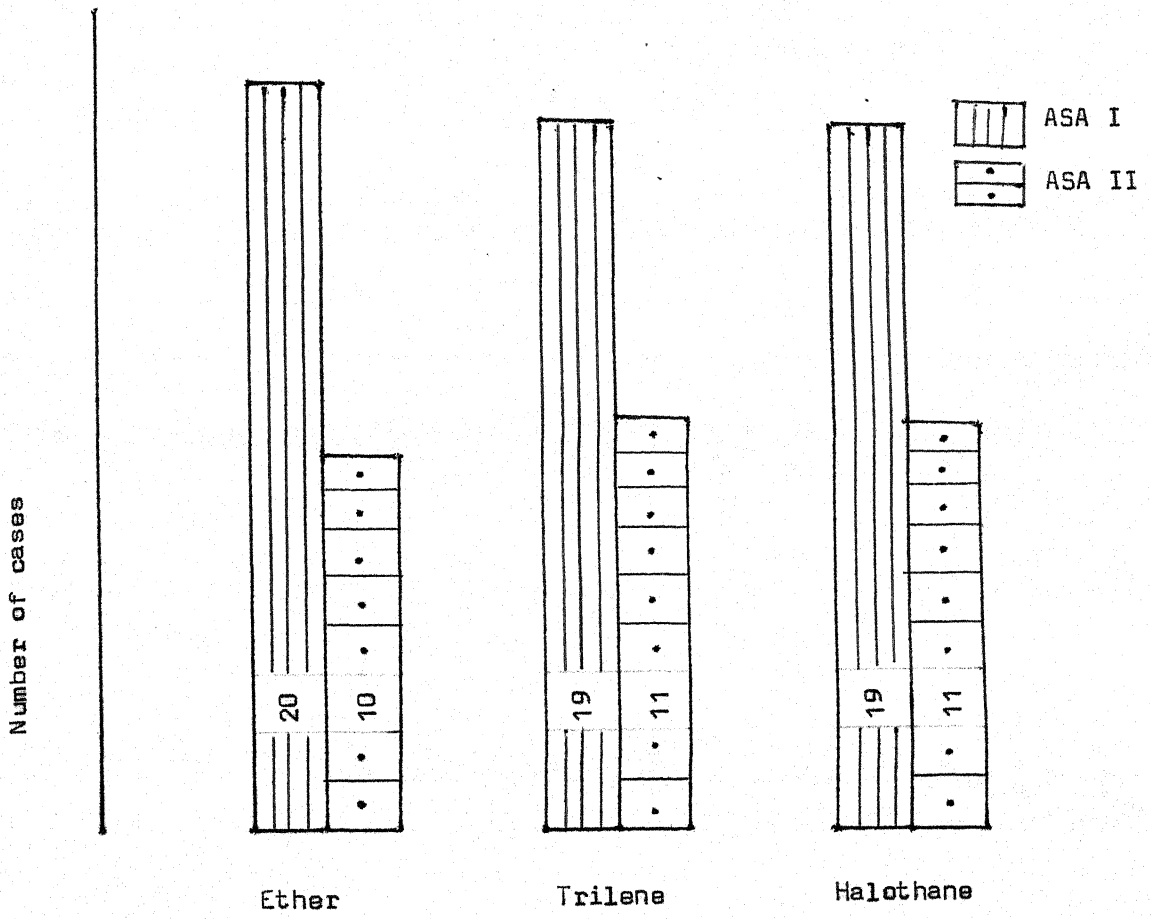

Fig.14- Showing number of cases according to ASA physical status in the various groups.

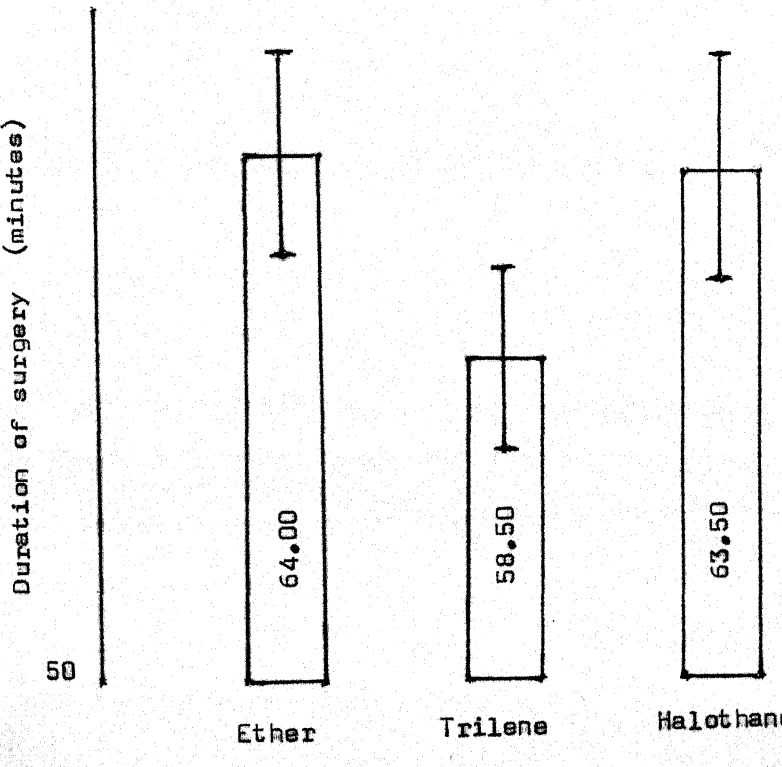

Fig.15- Showing mean duration (± S.E.) of surgery in the various groups.

TABLE - 4

Showing distribution of various operative procedures performed in different groups

Name of operation	Group I (Ether)	Group II (Trilene)	Group III (Halothane)
Abdominal hysterectomy	2	6	2
Appendicectomy	2	2	3
Exploratory laparatomy	8	3	6
Facial/Facio-maxillary injury	0	1	1
Fothergill's repair	1	0	1
Graciloplasty	4	2	2
Herniorrhaphy	3	2	2
Hysterotomy with tubal ligation	0	2	0
Limb surgery	6	6	4
Lumbar sympathectomy	0	0	2
Ophthalmic surgery	0	1	1
Ovariectomy	1	1	0
Prostatectomy	1	0	1
Skin grafting	0	1	1
Simple mastectomy	0	1	1
Simple mastoidectomy	2	2	1
Vagotomy with gastrojejunostomy	0	0	2
Total	30	30	30

Care was taken to represent a vast array of operations among the 30 cases alloted to each group (as is evident from the table). Yet, due to technical problems, it was not always possible to allot an exactly equal number of cases for some comparable operation in all the three groups.

TABLE – 5

Showing mean duration of operations (minutes) in various groups

Statistical parameter	Group I (Ether)	Group II (Trilene)	Group III (Halothane)
Mean	64.00	58.50	63.50
S.D. ±	14.70	13.27	16.10
S.E. ±	2.68	2.42	2.94

The mean operative duration (from skin to skin) was 64.00 ± 14.70, 58.50 ± 13.27 and 63.50 ± 16.10 minutes for the three groups. In other words, the duration of operation was nearly identical for all three groups.

TABLE - 6

Showing changes in blood sugar level (mg./dl.) in the various groups

		S_1 (Control)	S_2	S_3	S_4	S_5	S_6	S_7
ETHER	Mean	76.90	85.10	89.73	92.27	97.70	114.43	126.43
	S.D.±	10.83	11.26	12.54	13.50	13.12	19.95	20.01
	S.E.±	1.98	2.06	2.29	2.47	2.40	3.65	3.66
TRILENE	Mean	76.80	83.00	85.43	89.00	90.20	106.23	113.30
	SD ±	11.39	12.47	13.00	13.03	13.04	15.46	17.04
	S.E.±	2.08	2.28	2.37	2.38	2.38	2.82	3.11
HALOTHANE	Mean	71.23	77.37	79.33	83.27	85.40	96.33	110.63
	S.D. ±	10.49	10.67	10.95	12.25	12.63	15.74	20.36
	S.E. ±	1.91	1.95	2.00	2.24	2.31	2.88	3.72

The differences between values of S_2 and S_1 (i.e. the change caused during the procedure of intubation etc.) were (in mg./dl.) 8.20, 6.20 and 6.14 for ether, trilene and halothene groups respectively. The difference between S_5 and S_2 (i.e. change caused by the anaesthetic agent and technique after intubation) were (in mg./dl.) 12.60, 7.20 and 8.0$ respectively for the three groups.

The corresponding values (during intubation and there after) for trilene and halothane were nearly similar, while those of ether were far greater.

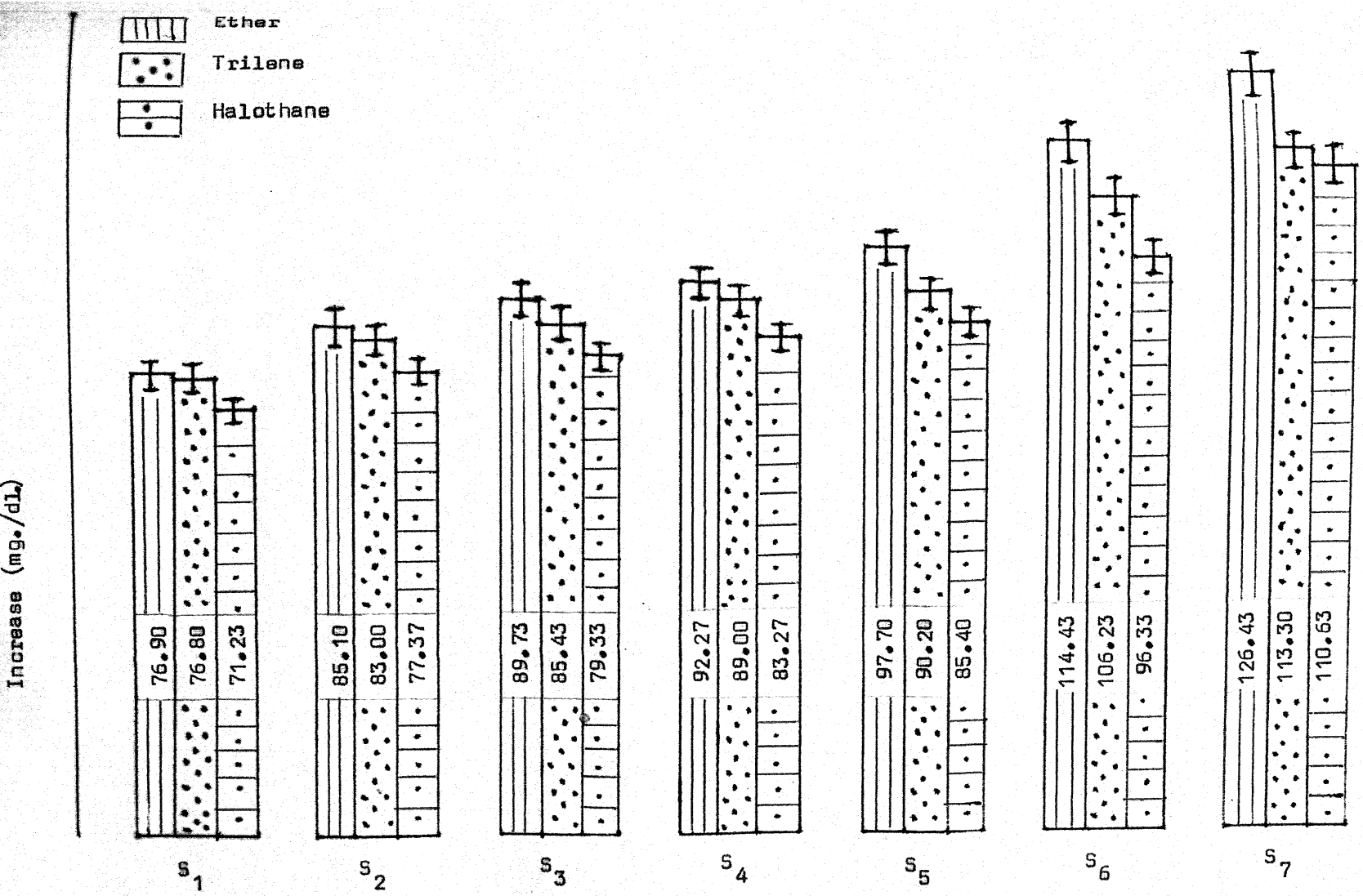

Fig.16- Showing mean changes (± S.E.) in blood sugar level in various groups.

TABLE - 7

Showing mean changes in blood sugar (mg./dl.) in subsequent samples among various groups:-

		ANAESTHESIA ALONE				SURGERY WITH ANAESTHESIA	
		Intubation	Anaesthesia beyond intubation				
		$S_2 - S_1$	$S_3 - S_2$	$S_4 - S_3$	$S_5 - S_4$	$S_6 - S_5$	$S_7 - S_6$
Ether	Mean	8.20	4.63	2.54	5.43	16.73	12.00
	%	10.66	5.44	2.84	5.88	17.12	10.49
Trilene	Mean	6.20	2.43	3.57	1.20	16.03	7.07
	%	8.07	2.93	4.18	1.35	17.77	6.66
Halothane	Mean	6.14	1.96	3.94	2.13	10.93	14.30
	%	8.62	2.53	4.97	2.56	12.80	14.84

The changes from one sample to another show an irregular pattern of increase during anaesthesia as well as during surgery with anaesthesia for all the three groups.

The percent increase was maximum during surgery followed by the percent increase during intubation in all the three groups.

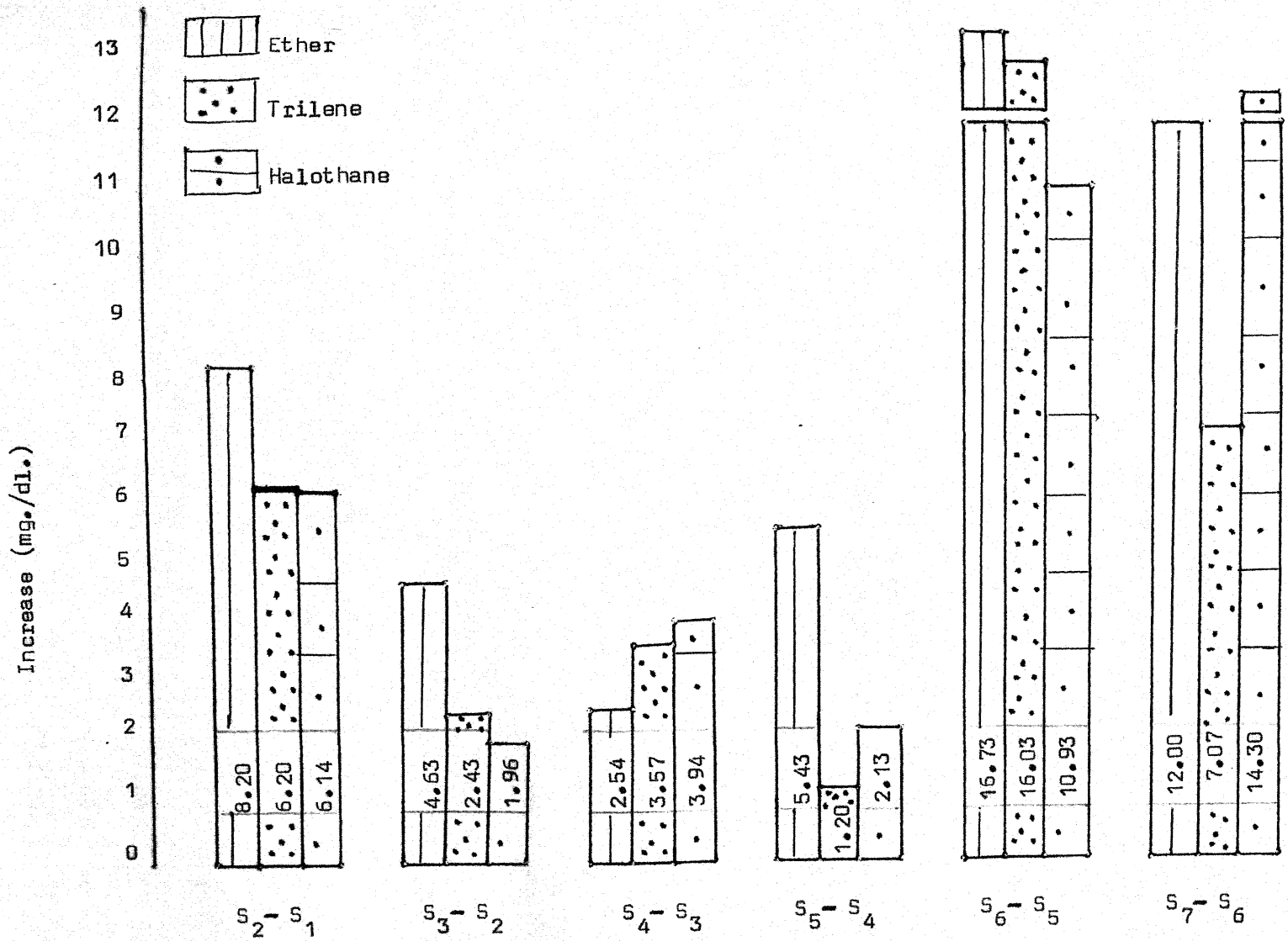

Fig. 17 - Showing mean increase from one samples to another in blood sugar in various groups.

TABLE - 8

Showing mean changes in blood sugar level (mg./dl.) over the control and their significance

	Samples	Increase over control	't' value	'p'	Significance	
ETHER	S_1 (Control)	-	-	-	-	
	S_1 & S_2	8.20	2.88	< 0.01	*	
	S_1 & S_3	12.83	4.26	< 0.001	*	*
	S_1 & S_4	15.37	4.90	< 0.001	*	*
	S_1 & S_5	20.80	5.33	< 0.001	*	*
	S_1 & S_6	37.53	9.45	< 0.001	*	*
	S_1 & S_7	49.53	12.45	< 0.001	*	*
TRILENE	S_1 (Control)	-	-	-	-	
	S_1 & S_2	6.20	2.01	< 0.01	*	
	S_1 & S_3	8.63	2.77	< 0.001	*	*
	S_1 & S_4	12.20	3.87	< 0.001	*	*
	S_1 & S_5	13.40	4.25	< 0.001	*	*
	S_1 & S_6	29.43	8.50	< 0.001	*	*
	S_1 & S_7	36.50	9.96	< 0.001	*	*
HALOTHANE	S_1 (Control)	-	-	-	-	
	S_1 & S_2	6.14	2.25	< 0.01	*	
	S_1 & S_3	8.10	2.93	< 0.001	*	*
	S_1 & S_4	12.04	4.10	< 0.001	*	*
	S_1 & S_5	14.17	4.75	< 0.001	*	*
	S_1 & S_6	25.10	7.42	< 0.001	*	*
	S_1 & S_7	39.40	9.90	< 0.001	*	*

* = Significant ** = highly significant

Intubation caused significant change in all the three groups. The changes at subsequent intervals (at 15, 30 & 45 minutes of anaesthesia and 20 & 45 minutes of surgery with anaesthesia) became highly significant in all the three groups.

TABLE - 9

Showing mean increase in blood sugar (mg./dl.) during various parts of anaesthesia alone among various groups:-

		ANAESTHESIA ALONE	
		Intubation ($S_2 - S_1$)	Beyond intubation ($S_5 - S_2$)
ETHER	Mean	8.20	12.60
	S.D. ±	2.81	4.44
	S.E. ±	0.51	0.81
	%	39.42	60.58
TRILENE	Mean	6.20	7.20
	S.D. ±	2.99	2.14
	S.E. ±	0.55	0.39
	%	46.27	53.73
HALOTHANE	Mean	6.14	8.03
	S.D. ±	4.57	3.93
	S.E. ±	0.83	0.72
	%	43.33	56.67

The procedure of intubation caused major change in only 5 minutes as compared to change caused by anaesthesia after intubation in 40 minutes in all the three groups. On the other hand, intubation caused nearly uniform change in all groups, but anaesthesia thereafter caused nearly double increase with ether than either with Trilene or with Halothane.

TABLE - 10

Showing effect of anaesthetic agent alone and surgery alongwith anaesthetic agent on blood sugar level (mg./dl.)

		Anaesthetic agent alone ($S_5 - S_1$)	Surgery with anaesthesia ($S_7 - S_5$)
ETHER	Increase	20.80	28.73
	S.D. ±	5.71	11.62
	't' value	5.33	6.72
	'p'	< 0.001	< 0.001
	Significance	Highly significant	Highly significant
TRILENE	Increase	13.40	23.10
	S.D. ±	3.86	11.89
	't' value	4.25	5.95
	'p'	< 0.001	< 0.001
	Significance	Highly significant	Highly significant
HALOTHANE	Increase	14.17	25.23
	S.D. ±	6.09	11.29
	't' value	4.75	5.93
	'p'	< 0.001	< 0.001
	Significance	Highly significant	Highly significant

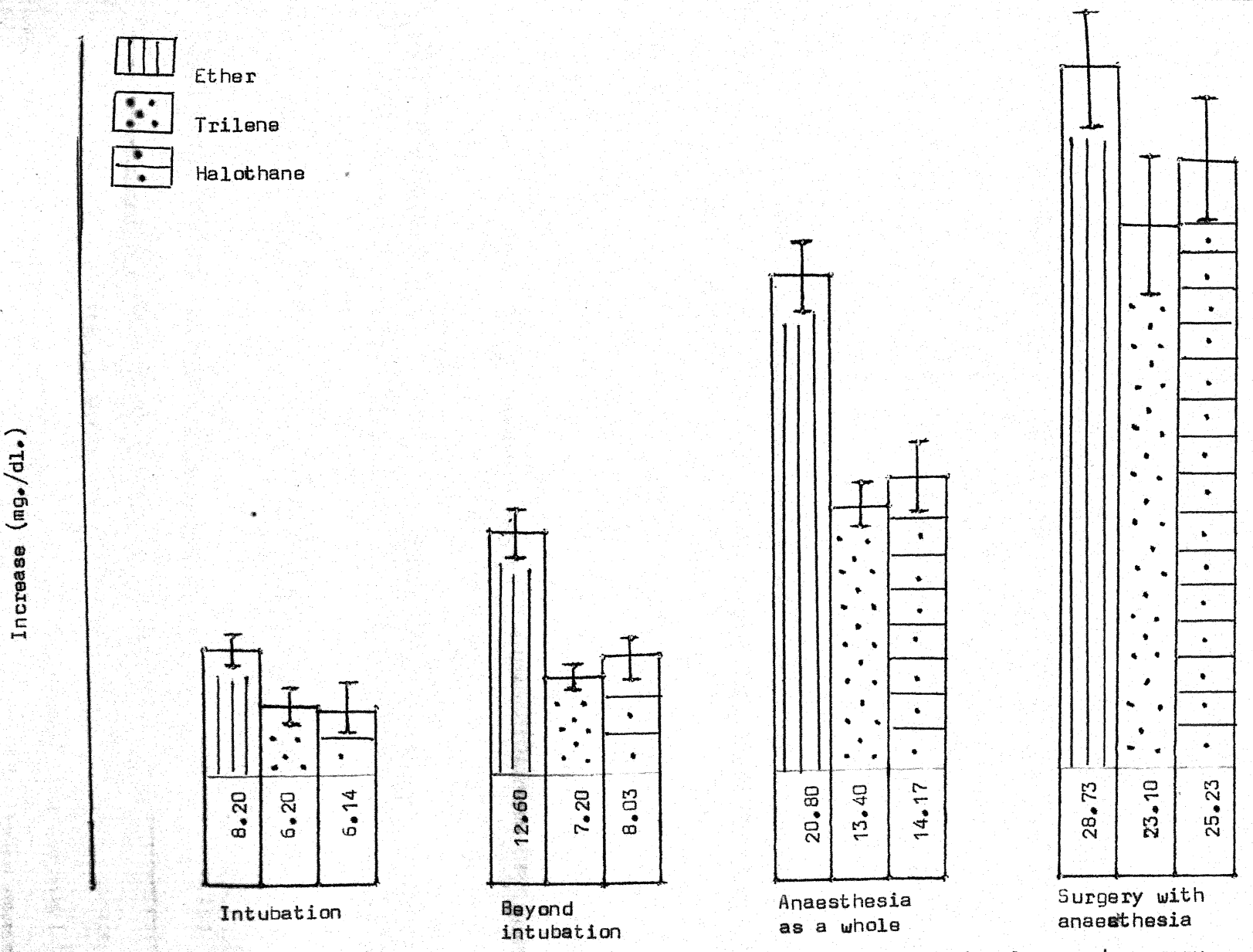

Fig. 18 - Showing mean changes (± S.E.) in blood sugar during anaesthesia alone and surgery with anaesthesia in various groups.

Among the anaesthetic agents, trilene and halothane caused nearly similar change while ether caused far greater change. But still all the three agents caused significant changes.

Surgery with anaesthesia caused dissimilar changes in the three groups. The change with ether group was maximum followed by groups of halothane and trilene respectively.

Surgery with anaesthesia caused much more increase as compared to that caused by anaesthesia alone in all groups.

TABLE – 11

Showing changes in blood FFA level (mEq/litre) in various groups

		S_1 (Control)	S_2	S_3	S_4	S_5	S_6	S_7
ETHER	Mean	0.616	0.721	0.764	0.853	0.925	1.265	1.441
	S.D. ±	0.095	0.097	0.112	0.115	0.132	0.218	0.254
	S.E. ±	0.017	0.078	0.020	0.021	0.024	0.040	0.046
TRILENE	Mean	0.600	0.662	0.680	0.732	0.777	1.068	1.224
	S.D. ±	0.079	0.081	0.089	0.097	0.094	0.208	0.255
	S.E. ±	0.014	0.015	0.016	0.018	0.017	0.038	0.047
HALOTHANE	Mean	0.632	0.704	0.724	0.773	0.776	1.060	1.282
	S.D. ±	0.098	0.100	0.112	0.132	0.134	0.305	0.363
	S.E. ±	0.018	0.018	0.020	0.024	0.025	0.025	0.067

The differences between values of S_2 & S_1 (i.e. change caused during the procedure of intubation etc.) were (in mEq/litre) 0.104, 0.062 and 0.072 for ether, trilene and halothane groups respectively.

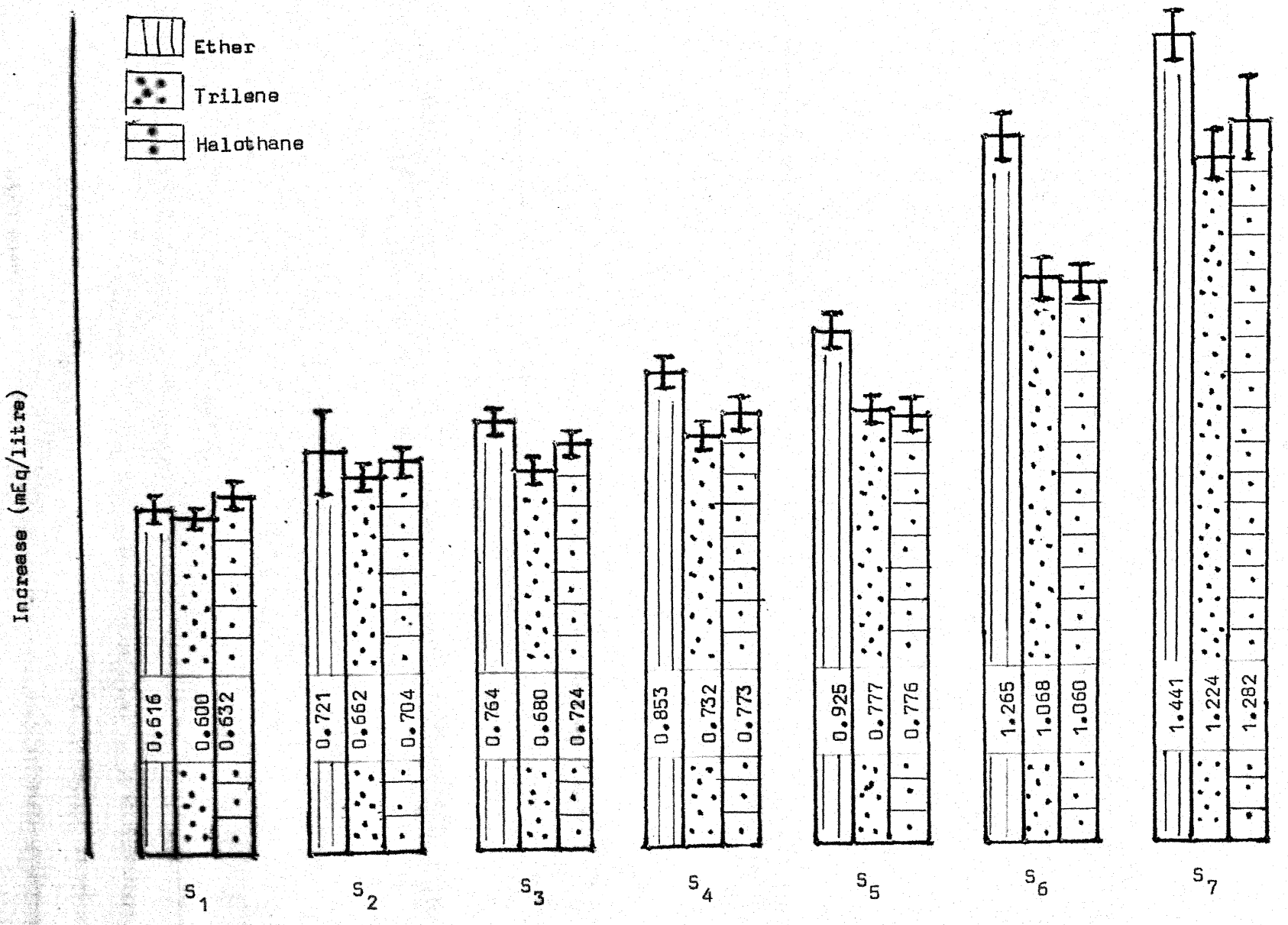

Fig. 19 - Showing mean changes (± S.E.) in blood FFA in various groups.

The difference between S_5 & S_2 (i.e. change caused by the anaesthetic agent and technique after intubation) were (in mEq/litre) 0.205, 0.115 and 0.072 respectively for the three groups.

The corresponding values during intubation were nearly similar for trilene and halothane but those for ether were far greater. The values during anaesthesia after intubation were dissimilar for all the three groups.

TABLE - 12

Showing mean changes in blood FFA (mEq/litre) in subsequent samples among various groups:-

		ANAESTHESIA ALONE				SURGERY WITH ANAESTHESIA	
		Intubation	Anaesthesia beyond intubation				
		$S_2 - S_1$	$S_3 - S_2$	$S_4 - S_3$	$S_5 - S_4$	$S_6 - S_5$	$S_7 - S_6$
ETHER	Mean	0.104	0.043	0.089	0.072	0.340	0.176
	%	16.88	5.96	11.65	8.44	36.76	13.91
TRILENE	Mean	0.062	0.018	0.052	0.045	0.291	0.156
	%	10.33	2.72	7.64	6.15	37.45	14.61
HALOTHANE	Mean	0.072	0.020	0.049	0.003	0.284	0.222
	%	11.39	2.84	6.77	0.39	36.60	20.94

The changes from one sample to another show an irregular pattern of increase during anaesthesia as well as during surgery with anaesthesia in all the three groups. Maximum percent increase was observed during surgery followed by intubation in all groups.

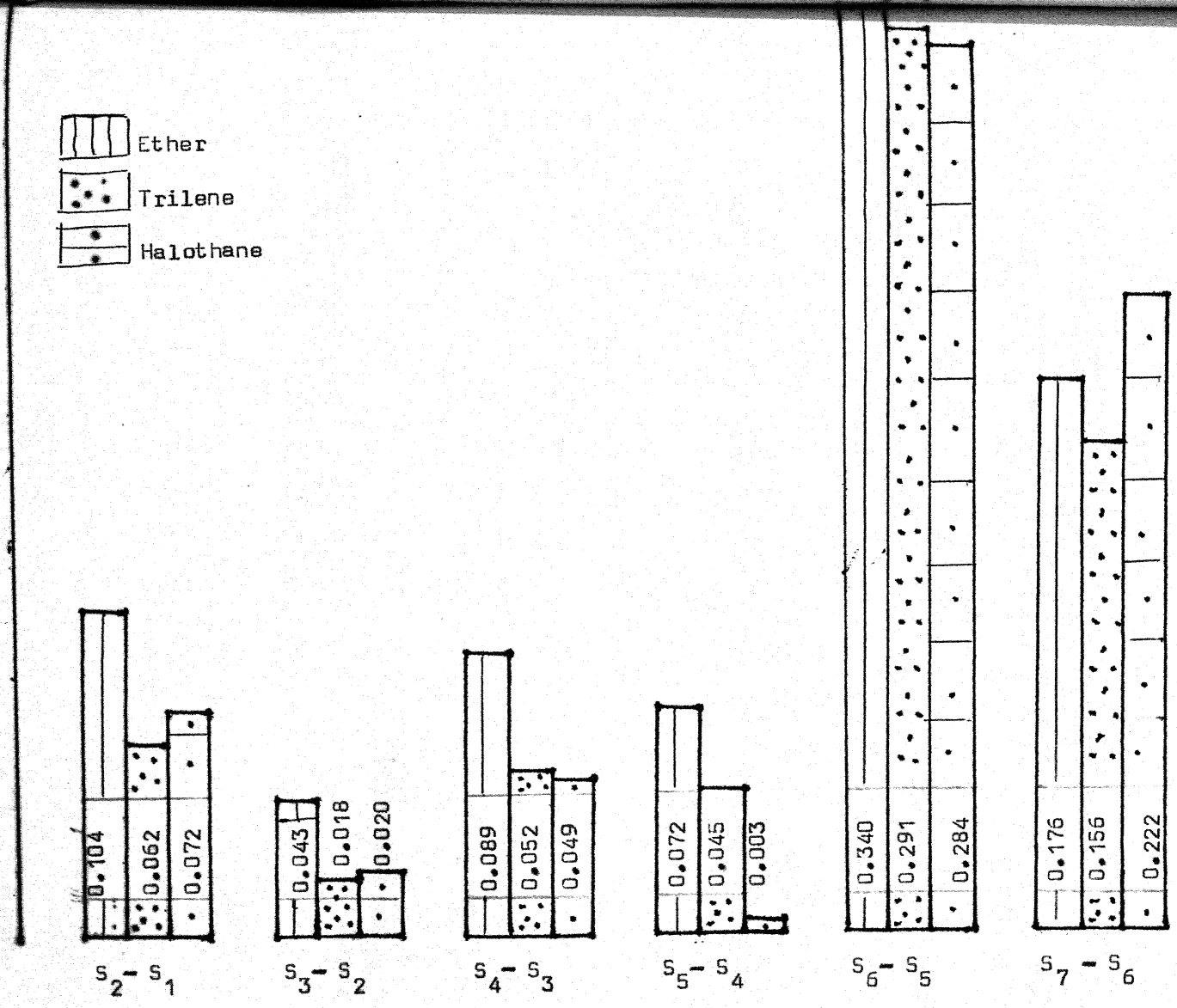

Fig. 20- Showing mean increase from one sample to another in blood FFA in various groups.

TABLE – 13

Showing mean changes in blood FFA level (mEq/litre) over the control and their significance

	Samples	Increase over control	't' value	'P'	Significance	
ETHER	S_1 (Control)	–	–	–	–	
	S_1 & S_2	0.105	4.24	< 0.001	*	*
	S_1 & S_3	0.148	5.54	< 0.001	*	*
	S_1 & S_4	0.237	8.75	< 0.001	*	*
	S_1 & S_5	0.309	10.54	< 0.001	*	*
	S_1 & S_6	0.649	16.10	< 0.001	*	*
	S_1 & S_7	0.825	18.33	< 0.001	*	*
TRILENE	S_1 (Control)	–	–	–	–	
	S_1 & S_2	0.062	3.01	< 0.01	*	
	S_1 & S_3	0.080	3.69	< 0.001	*	*
	S_1 & S_4	0.132	5.81	< 0.001	*	*
	S_1 & S_5	0.177	7.94	< 0.001	*	*
	S_1 & S_6	0.468	12.64	< 0.001	*	*
	S_1 & S_7	0.624	14.48	< 0.001	*	*
HALOTHANE	S_1 (Control)	–	–	–	–	
	S_1 & S_2	0.072	2.82	< 0.01	*	
	S_1 & S_3	0.092	3.39	< 0.001	*	*
	S_1 & S_4	0.141	4.75	< 0.001	*	*
	S_1 & S_5	0.144	4.81	< 0.001	*	*
	S_1 & S_6	0.428	8.23	< 0.001	*	*
	S_1 & S_7	0.650	10.93	< 0.001	*	*

* = Significant ** = highly significant

Intubation caused highly significant increase in ether group but only significant increase in trilene and halothane group.

The changes at subsequent intervals (at 15, 30 & 45 minutes of anaesthesia and 20 & 45 minutes of surgery with anaesthesia) became highly significant in all the three groups.

TABLE – 14

Showing mean increase in blood FFA (mEq/litre) during various parts of anaesthesia alone among the various groups:-

		ANAESTHESIA ALONE	
		Intubation ($S_2 - S_1$)	Beyond intubation ($S_5 - S_2$)
ETHER	Mean	0.104	0.205
	S.D. ±	0.043	0.070
	S.E. ±	0.008	0.013
	%	33.66	66.34
TRILENE	Mean	0.062	0.115
	S.D. ±	0.030	0.055
	S.E. ±	0.005	0.010
	%	35.03	64.97
HALOTHANE	Mean	0.072	0.072
	S.D. ±	0.046	0.052
	S.E. ±	0.008	0.009
	%	50.00	50.00

The procedure of intubation caused major change in only 5 minutes as compared to change caused by anaesthesia thereafter

in 40 minutes in all the three groups.

On the other hand, intubation caused nearly uniform change in all groups, but anaesthesia thereafter caused change in the ratio of 6 : 3 : 2 in ether, trilene and halothane groups respectively.

TABLE - 15

Showing effect of anaesthetic agent alone and surgery alongwith anaesthetic agent on blood FFA level (mEq/litre)

		Anaesthetic agent alone ($S_5 - S_1$)	Surgery with anaesthesia ($S_7 - S_5$)
ETHER	Increase	0.309	0.516
	S.D.±	0.084	0.207
	't' value	10.54	10.36
	'p'	< 0.001	< 0.001
	Significance	Highly significant	Highly significant
TRILENE	Increase	0.177	0.447
	S.D.±	0.061	0.222
	't' value	7.94	9.93
	'p'	< 0.001	< 0.001
	Significance	Highly significant	Highly significant
HALOTHANE	Increase	0.144	0.506
	S.D.±	0.084	0.274
	't' value	4.81	7.89
	'p'	< 0.001	< 0.001
	Significance	Highly significant	Highly significant

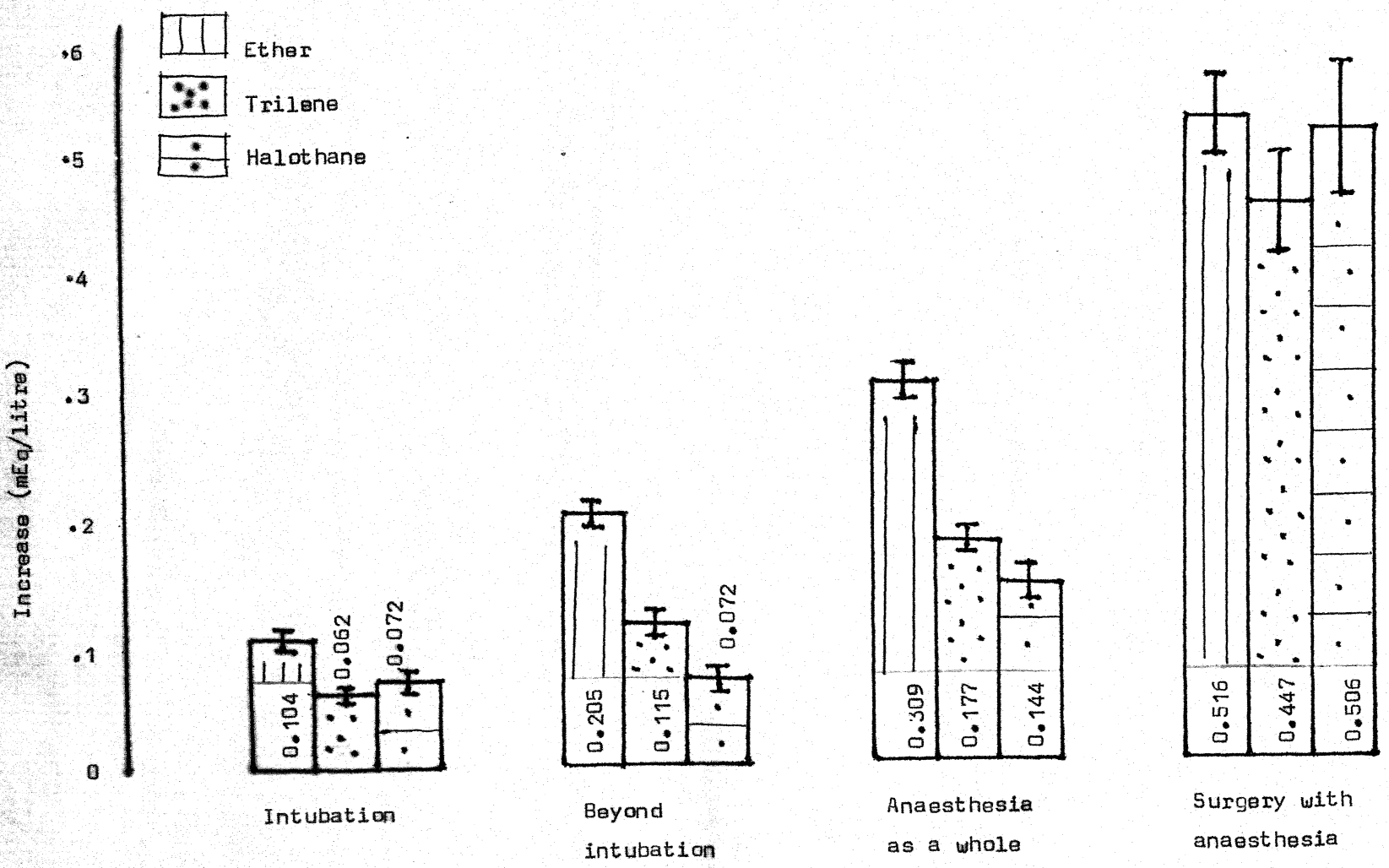

Fig. 21 - Showing mean changes (± S.E.) in blood FFA during anaesthesia alone and surgery with anaesthesia in various groups.

Among the anaesthetic agents, trilene and halothane caused nearly similar changes (i.e. 0.177 ± 0.061 and 0.144 ± 0.084 mEq/litre) while ether caused far greater change (i.e. 0.309 ± 0.084 mEq/litre) but still all the three agents caused significant changes.

Surgery with anaesthesia caused nearly similar changes in ether and halothane groups (i.e. 0.516 ± 0.207 and 0.506 ± 0.274 mEq/litre) but the trilene group showed a little less change (i.e. 0.447 ± 0.222 mEq/litre).

The change caused by the surgery and anaesthesia was much greater than that caused by anaesthesia alone in all the three groups.

DISCUSSION

D I S C U S S I O N

George L. Blackburn and Robert R. Wolfe, once in 1981, wrote thus :-

" The spontaneous changes in carbohydrate, lipid, protein and energy metabolism after injury are a normal occurance and represent one of Nature's most elaborate and concerted efforts towards survival. To regard the response of the body to injury as " pathological" or as a "functional wasting" is to overlook its elegance and to fail to understand the mechanisms. Rather, these mechanisms should serve as a framework for designing fluid, electrolyte and nutritional support. Only when the severity of illness results in organ failure or systemic sepsis, does this metabolic response collapses. Proper use of nutritional support can considerably prevent these adverse effects of organ failure and sepsis."

Almost at the same time (in 1981 , to be precise) Celine Traynor and G.M. Hall commented :-

" The neuroendocrine response to trauma appears to have evolved to assist survival in a more primitive environment by providing appropriate substrates to maintain vital functions. However in modern anaesthetic and surgical practice, where severe physiological disturbances are prevented or rapidly treated with prompt administration of suitable substrates, any benefits of this response are no longer apparent."

These are only few from the galaxy consisting, among others, celebrities like S.P. Allison (1969), L.H. Cooperman (1970), R.S.J. Clarke (1970), T. Oyama & T. Takazawa (1970), R.G. Merin (1971), N. Yoshimura (1971), A. Makelainen (1974), G.R. Gode (1977), K. Pandey (1977, 82) and N. Bose (1981) —— who have differed on some particular topic at one time or other. One is left really amused and aghast to see these professional stalwarts expressing such diabolically different opinions on same subject.

There is an ancient chinese proverb that whenever there exists some doubt, it is al ways better to confirm the things by doing a lot of legwork and a bit of brainwork.

So, with this objective being the motive force; this observer, in all his humbleness, undertook the present study.

The cellular metabolic response to illness, injury and infection is dependent upon the available fuel sources and their utilization (Blackburn et al, 1973; Clowes et al, 1974). The metabolic events occuring immediately after injury (upto 48 hours) are dominated by local and systemic effects of hormones, particularly catecholamines (Clowes, 1976; Wilmore et al, 1976). Catecholamines promote calorigenesis, glycogenolysis and lipolysis. Simultaneously insulin activity is suppressed. Insulin plays a key role in regulating energy metabolism by increasing the rate of glucose utilization and controlling the rate of FFA release from adipose tissue. It lowers cAMP level in adipose tissue and has a direct antagonist action on lipase activity (Sutherland et al, 1968). Concommitant release of growth hormone, glucagon and glucocorticoids also inhibit activity of insulin.

The overall objective of these changes is to maintain the body cell mass as constant as possible and also maintenance of proper ATP : ADP ratios and NAD : NADH oxidation : reduction states (Blackburn, 1977).

The anaesthetic hyperglycemia and hyperlipemia are mainly results of excessive hepatic glycogenolysis and adipose tissue lipolysis brought about by sympathoadrenal stimulation. The extent of this response will, therefore, vary with the sympathomimetic activity of the anaesthetic agent used. Hence the present work aims to observe the effects of inhalational agents on carbohydrate and lipid metabolism by studying changes in blood sugar and FFA.

Coming to the present series of study, the 90 patients studied by us, were divided into 3 groups (I, II & III) of 30 each according to the anaesthetic agent given (table - 1). An equal number of patients in each group eliminated the possible numerical superiority of one group over the other.

Furthermore in each group itself, the ratio of male : female patients was kept approximately 3 : 2 (table - 1). This obviated the need to take into consideration, the sex-dependent difference (if any), in response to anaesthesia and/or surgery.

Like-wise no obese or emaciated person was included in the present study (table - 2; fig - 13), as the nutritional status is known to significantly affect the blood glucose and FFA level (Owen et al, 1967; Newsholme, 1977; Hansen and Parsons, 1978; Stanley, 1981).

The present study showed nearly similar weights for males

(50.54 - 52.29 kg.) and for females (42.33 - 45.64 kg.) in the three groups. This obviated the influence of nutritional status on metabolism (table - 2; fig - 13).

As previous trauma, injury or infection result in significant alterations in the hormonal and metabolic status of the patients (Cuthbertson, 1970; Blackburn et al, 1973; 1981; Wilmore et al, 1976; Stanley, 1981), care was exercised to include only those patients in the present study who qualified for ASA physical status I or II (i.e. who were in good health and were likely to have a minimal pre-existing metabolic derangement) as shown in table - 3, fig - 14.

As a further precaution, almost an equal number of patients belonging either to ASA I or ASA II were included in all the 3 groups (i.e. 20/10, 19/11 and 19/11) and the ratio between cases of ASA I and those of ASA II was approximately 2 : 1 in all the groups(table -3; fig - 14). This meant that previous trauma or injury will not unduly affect any particular group.

Various workers have attempted different modus operandi in an attempt to study the effect of surgery on blood sugar and FFA. Either they included patients undergoing variable surgery i.e. body surface —— , thoracic ——, limb —— or intraabdominal surgery (Cooperman, 1970; Clarke, 1970; Clarke et al, 1970; Dev et al, 1977; Singh et al, 1977; Bose and Biswas, 1981) or they fixed this variable i.e. they chose only some particular type of surgery during their study (Sharma, Basu & Pandey, 1977; Gupta, Jain & Pandey, 1982).

In our series, to eliminate the significant difference between the extent of metabolic response seen during different types of surgery, the distribution of different operations was kept nearly uniform

(table - 4) but unforeseen technical problems beyond reasonable control of this observer, sometimes made the task rather difficult.

It is a well- known entity that the extent of metabolic and hormonal response is directly proportionate to the severity of injury or operative trauma (Annamunthodo, 1958; Singhal et al, 1979; 1982; Stanley, 1981). The severity of trauma depends, among other factors, on the duration of operation. Oyama et al (1971) found that an exposure of less than 60 minutes is also associated with metabolic and hormonal changes.

Thus in order to avoid and obviate any fallacious results, the mean operative duration (from skin to skin) was kept nearly identical (i.e. 58.50 - 64.00 minutes) for all the three groups (table - 5; fig - 15). This made possible a comparision to be carried out between the various groups for the comparable samples obtained during operative procedure itself (tables - 7, 10, 12 & 15; figs - 17, 18, 20 & 21). It further made possible a comparision between the changes caused by anaesthesia alone and changes caused by surgery with anaesthesia, because with drawal of samples was upto 45 minutes during both procedures (tables - 10 & 15; figs - 18 & 21).

During anaesthesia and surgery,there are several other factors operating beside the anaesthetic agent, which lead to sympathoadrenal stimulation. Among these are hypoxia (Johnstone, 1949), hypercarbia, hypotension (Wright, 1970) and handling of viscera (Dixit, 1972). In addition to these, pre-operative anxiety and emotional stress in patients awaiting surgery have been held responsible for rise in blood sugar and FFA levels (Allison, Tomlin and Chamberlain, 1969;

Merin et al, 1971; Gupta, Jain & Pandey, 1982). Excitement of induction and vasopressors given during the operation also play some role. All these factors may contribute to the stimulation of sympathoadrenal system resulting in the release of catecholamines and mobilization of glycogen from liver and FFA from adipose tissue.

Sedative premedicants, therefore, supress this response which is mediated through the hypothalamus (Sharma, Basu & Pandey, 1977; Gupta, Jain & Pandey, 1982).

In order to achieve these objectives, every patient was carefully told about the anaesthetic and the operative procedure, properly assured and given lorazepam 2 - 4 mg. orally in the night preceding the operation.

Our primery aim was to obtain the basal values of blood glucose and FFA (when the patient was comparatively stabilized and free from anxiety or fear). These basal values were required to serve as the control, with which the subsequent samples were to be compared statistically (tables- 8 & 13).

Various workers have used samples taken many hours before operation (Sharma, Basu & Pandey, 1977; Bose and Biswas, 1981) or after adequate sedation (Cooperman, 1970; Clarke, 1970; Dev et al, 1977; Singh et al, 1977) as the control. Some other workers (Paul and Bhattacharya, 1977) have also used sample values obtained from some normal person and compared them with those of the patients. This last method suffered from the obvious disadvantage that values of a normal person are hardly comparable with those of another person (i.e. patients).

The control values for blood sugar in the present series

were 76.90 ± 10.83; 76.80 ± 11.38 and 71.23 ± 10.49 mg./dl. for the ether, trilene and halothane groups respectively(table - 6; fig- 16). These values are in accordance with those obtained by Basu et al, (1977), Singh et al (1977), Sharma et al (1977), Singhal et al (1979) and Gupta et al (1982); but differ from those obtained by Clarke (1970), Clarke et al (1970) and Cooperman (1970).

The control values for plasma FFA in the present series were 0.616 ± 0.095, 0.600 ± 0.079 and 0.632 ± 0.098 mEq/litre for the ether, trilene and halothane groups respectively (table - 11; fig - 19). In other words, values were nearly identical for all groups.

These values are in accordance with those obtained by Cooperman (1970) and Bose et al (1981); but differ from those of Clarke et al (1970), Sharma, Basu and Pandey (1977), Singhal et al (1979) and Gupta et al (1982).

One possible explanation for the difference in these values may be that, some of the workers (Cooperman, 1970; Clarke, 1970 and Clarke et al, 1970) have studied white coloured population in western countries and thus some racial or geographical factor may be operative.

The other attractive possible reasons may be fluctuations in the emotional status of patient (anxiety and apprehension leading to increased sympathoadrenal activity), the time of obtaining samples, duration of starvation, type of premedication given or the difference in techniques employed for estimation of blood sugar or plasma FFA (Cooperman, 1970; Clarke, 1970; Dev et al, 1977; Sharma et al, 1977; Singhal et al, 1979; 1982; Gupta et al, 1982).

The procedure of intubation is known to be most stormy one during anaesthesia (Singhal et al, 1982) and is associated with

considerable metabolic and hormonal changes; catecholamine level suddenly rises markedly and the occurance of cardiac dysrhythmia is most common.

In the present series, intubation caused significant ($P < 0.01$) increase of 6.14 - 8.20 mg./dl. over control values in blood sugar in a very short period of 5 minutes. This increase was nearly uniform (8.07% - 10.66%) over the control irrespective of the anaesthetic agent used (table - 8; Fig - 18).

These findings are in harmony with those of Clarke (1970), Dev et al (1977), Sharma et al (1977), Singh et al (1977) and Gupta et al (1982).

The corresponding values for plasma FFA during intubation recorded a significant increase ($P < 0.01$, but for ether $P < 0.001$) of 0.062 - 0.104 mEq/litre in the same period of 5 minutes. This increase was to the tune of 33.66% - 50.00% over the control regardless of the anaesthetic agent given (table - 13; fig - 21).

These finding are in complete unisone with those recorded by Clarke et al (1970), Sharma et al (1977), Bose and Biswas (1981) and Gupta et al (1982); but differ from those of Cooperman (1970) and Singhal et al (1979).

Possible explanation for these differences may be due to different premedications (quinalbarbitone by Cooperman, 1970) and different methods of estimation (Duncombe's method , 1963 used by Singhal et al , 1979 and Trout's modification of Dole's method, 1960 used by Cooperman, 1970) as compared to oral lorazepam over night and Millian Novak's technique, 1956 in the present series.

Griffiths (1953) and Annamunthodo (1958) attributed the

hyperglycemia caused by ether anaesthesia to direct action of the anaesthetic on liver leading to glycogenolysis. Increased sympathoadrenal activity results in significant rise in the level of plasma adrenaline and noradrenaline both (Elliot et al, 1968; Black et al, 1969; Singhal et al, 1982).

Also ether is one of the strongest stimulants of adrenocortical activity (Vandam & Moore, 1960) in an exposure of less than 60 minutes (Oyama et al, 1971) leading to a resistance against insulin. It also interferes with the cellular metabolic processes (Cohen et al, 1972).

All these processes result in marked hyperglycemia (Brewster et al, 1952; Cullingford, 1966; Oyama et al, 1971) and acting via cAMP- dependent lipase-system (Sutherland et al, 1968), to increased lipolysis and marked rise in plasma FFA level (Henneman et al, 1961; Oyama et al, 1971; Singhal et al, 1979).

Trichloroethylene, on the other hand, raises the plasma levels of the catecholamines (Dixit, 1972; Lakshmi et al, 1973; Dev et al, 1977; Singh et al, 1977) and thereby enhances mobilization of tissue glycogen and triglycerides leading to hyperglycemia (Krantz and Carr, 1965; Dixit, 1972). Olson and Spencer (1968) observed that this agent also interferes with cellular metabolic processes and this may further contribute to the already raised levels of blood sugar and plasma FFA.

Halothane, not to be outdone and outsmarted, strives hard to produce a small rise in plasma catecholamines (Black et al, 1962; Elliot et al, 1968; Singhal et al, 1982). It also inhibits the glycolytic enzymes (Schweizer et al, 1969) and cellular uptake of

glucose (Green , 1965; Ngai, 1972), depresses FFA uptake by the myocardium (Merin et al, 1969) and suppresses activity of insulin (Aynsley-Green et al, 1973). Makelainen (1974) observed an increase in catecholamines level leading to increased mobilization of hepatic glycogen and adipose tissue triglycerides with resultant elevation in blood sugar (Allison et al, 1969; Merin et al, 1971; Oyama et al, 1971; Lakshmi et al, 1973; Makelainen, 1974 and Gupta et al, 1982) and in plasma FFA (Cooperman, 1970; Merin et al, 1971; Makelainen, 1974; Gupta et al, 1982).

Thus we can see that there are some common factors with all the three inhalational agents used, which lead to increased level of blood sugar and plasma FFA. These are :-

1. Only partial (and not complete) suppression of afferent stimuli like pain etc., going to cerebral cortex and hypothalamo - mesencephalic complex even during deep anaesthesia.
2. Stimulation of beta- adrenergic receptors leading to variable but definite increase in the levels of plasma catecholamines in an attempt to offset the depressant effects of anaesthetic agent (Black et al, 1969).

(N.B. - The body metabolic mechanisms are so sensitive that even a very small increase in plasma catecholamine levels results in a far greater mobilization of glycogen and triglycerides according to Rube Gold berg sequence).

3. Abolition of powerful antidiabetogenic and antilipolytic effects of insulin (the activity of which is suppressed to a variable extent)

4. Un-restrained activity of glucagon and cortisol etc.

5. Interference with the cellular metabolic processes (glycolysis, oxidative phosphorylation, electron transfer etc.).

In our study, anaesthesia with ether (in absence of surgery) showed a pattern of constant rise at various time intervals and the quanta of increases were highly significant ($P < 0.001$) for both blood sugar and plasma FFA (tables - 7, 8, 12 & 13; figs - 17 & 20).

Halothane and trilene also followed the same pattern, though on a much smaller scale. But they did show a similar trend of constant rise at subsequent time intervals and these raised values were highly significant ($P < 0.001$) for both blood sugar and plasma FFA (tables - 7, 8, 12 & 13; figs - 17 & 20).

Similar findings were noted by the various workers as mentioned earlier.

An interesting feature to emerge during the present study was that (because intubation causes nearly similar quanta of increase in blood sugar and plasma FFA in all types of general anaesthesia —— inhalational, muscle relaxants or neuroleptanaesthesia etc.) if we deduct the change caused by intubation procedure from the total change caused by anaesthesia alone, then the change caused by anaesthesia (minus intubation) were far too less (7.20 - 12.60mg./dl. for blood sugar; 0.072 - 0.205 mEq/litre for plasma FFA) as compared to that caused by anaesthesia with surgery (23.10 - 28.73 mg./dl. for blood sugar; 0.447 - 0.516 mEq/litre for plasma FFA) for all the three agents(tables - 9, 10, 14 & 15; figs - 18 & 21).

Possible explanations for this may be that once the stormy period of intubation is over (and provided that hypoxia, hypercarbia

& too light or too deep a plane of anaesthesia are avoided) there are hardly any stimuli to result in an alarm reaction (as depicted in fig - 4) to result in excessive mobilization of glycogen or adipose triglycerides and consequently there are little changes during anaesthesia (beyond intubation).

The total changes caused by anaesthesia without surgery were; in ether series (20.80 mg./dl. for blood sugar ; 0.309 mEq/litre for plasma FFA), in trilene series (13.40 mg./dl. for blood sugar; 0.177 mEq/litre for plasma FFA) and in halothane series (14.17 mg./dl. for blood sugar; 0.144 mEq/litre for plasma FFA) as shown in tables - 10 & 15 and figs - 18 & 21 .

All these changes were highly significant ($P < 0.001$) for all the three agents, although the 't' values showed fluctuations (4.25 - 5.33 for blood sugar; 4.81 - 10.54 for plasma FFA) (tables - 10 and 15).

As is apparent from careful perusal of above data, the maximum changes were seen with ether anaesthesia in both blood sugar and plasma FFA while trilene and halothane caused more or less similar changes in both these parameters.

The possible explanation is that there are some common factors operating during any type of general anaesthesia (as mentioned earlier) and they cause a certain amount of mandatory increase. But besides these, the most important factors for producing metabolic changes are the degree of sympathomimetic activity of the agent used & the capacity of that agent to suppress the activity of insulin. Ether is the most potent inhalational agent causing sympathetic stimulation and some degree of insulin suppression (Singhal, et al, 1979; Singhal et al, 1982).

Trilene is associated with remarkable cardiovascular stability (Kohli, Punnoose, Srihari & Gode, 1977) and some vagal stimulation (Holmes et al, 1962; Prior et al, 1965), thus implying that sympathomimetic activity is not much with this agent.

Halothane on the other hand, associated with some degree of central autonomic paresis & ganglionic blockade, nevertheless does cause some sympathomimetic activity (Singhal et al, 1982).

Thus the nearly similar but smaller changes caused by trilene and halothane as compared to ether in the present study are easily accounted for.

Anaesthesia with surgery, on the other hand, is associated with marked degree of sympathomimetic activity (Clarke et al, 1970; Halter et al, 1977; Nistrup Madsen et al, 1976; 1978; Engquist et al, 1980; Clutter et al, 1980) and increased activity of catabolic hormone glucagon in presence of decreased activity of key anabolic hormone insulin (Stanley, 1981), Handling of vital organs (Dixit, 1972) and only partial suppression of pain stimuli even in deep anaesthesia.

Thus, when all these factors combine togather to tear apart the citadel of metabolic integrity, it is no wonder that the results are simply devastating.

Therefore it is hardly surprising to see that in our study, surgery with anaesthesia, accounted for much greater changes (23.10 - 28.73 mg./dl. for blood sugar; 0.447 - 0.516 mEq/litre for plasma FFA) which were nearly uniform for all the agents ('t' value = 5.93 - 6.72 for blood sugar and 7.89 - 10.36 for plasma FFA) and were highly significant ($P < 0.001$) in all the three groups (tables - 10 & 15; figs - 18 & 21).

These observations are in excellent harmony with those of Clarke(1970), Clarke et al (1970), Singh et al (1977), Sharma et al (1977), Singhal et al (1979), Bose and Biswas (1981) and Gupta, Jain & Pandey (1982). These findings are understandable and can be easily accounted for, on the strength of the foregoing texts.

If we arrange the three agents in a descending order according to their capacity to cause changes, then the sequence for blood sugar becomes :-

I. Ether II. Halothane III. Trichloroethylene;

while that for plasma FFA becomes :-

I. Ether II. Trichloroethylene III. Halothane.

As a fitting finale to the whole show, J.C. Stanley (1981) walked away with an Oscar award for his splendid epilogue :-

> "Di- ethyl ether is unique among the inhalational agents in causing a liberation of glucogenic hormones other than catecholamines, as well as raising the blood sugar, in producing lactic acidosis and in failing to lower the elevated FFA level."

CONCLUSIONS

CONCLUSIONS

With the present series of study drifting towards its end, on the basis of the observations made and the inferences derived therefrom, let us precisely enumerate the conclusions as under :-

1. Anaesthesia alone and anaesthesia with surgery both caused highly significant increases ($P < 0.001$) in blood sugar and plasma FFA levels in all groups.
2. The quantum of increase was much greater (23.10 - 28.73 mg./dl. for blood sugar ; 0.447 - 0.516 mEq/litre for plasma FFA) during anaesthesia with surgery than that (13.40 - 20.80 mg./dl. for blood sugar ; 0.144 - 0.309 mEq/litre for plasma FFA) during anaesthesia alone.
3. The procedure of intubation, being the most stormy one, accounted for a major portion of total increase in blood sugar and plasma FFA irrespective of the inhalational agent employed.
4. During anaesthesia alone, the procedure of intubation etc. caused much more increase (39.42% - 46.27% and 33.66% - 50.00% of total increase) as compared to that caused by the rest of anaesthesia alone (53.73% - 60.58% and 50.00% - 66.34% of total increase) in blood sugar and plasma FFA respectively in all groups, if we compare the relative duration of both procedures (i.e. 5 minutes and 40 minutes respectively).
5. All the three inhalational agents used (i.e. ether, trichloroethylene and halothane) resulted in highly significant increases($P < 0.001$) in blood sugar and plasma FFA.
6. The quantum of increase in blood sugar was maximum with ether (20.80 mg./dl.), while trilene and halothane did not differ much (13.40 and 14.17 mg./dl. respectively).

7. Taking into consideration the plasma FFA, the quantum of increase was again maximum with ether (0.309 mEq/litre), which was much more than the nearly similar increase (0.144 and 0.177 mEq/litre respectively) caused by trilene and halothane.

8. If we deduct the change caused by intubation (which is compulsorily caused during all types of general anaesthesia — inhalational, muscle relaxants, neurolepts etc.) from the total increase, then all the three inhalational agents caused much less increase in both blood sugar and plasma FFA as compared to the anaesthesia with surgery.

9. Arranging in the descending order (according to the quantum of increase caused by each inhalational agent), the sequence for blood sugar was — 1. Ether, 2. Halothane and 3. Trichloroethylene; while that for plasma FFA was — 1. Ether, 2. Trichloroethylene and 3. Halothane.

... A D I E U !

(till we meet again).

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